# CLINICAL EFFICACY REVIEW
# NONMALIGNANT INDICATIONS

| | |
|---|---|
| Application Type | BLA |
| Division / Office | DCEPT / OCTGT |
| Reviewer | John E. Hyde, Ph.D., M.D. |
| Supervisory Reviewer | Wilson W. Bryan, M.D. |
| Review Completion Date | November 3, 2011 |
| Established Name | Hematopoietic progenitor cells – cord |
| Therapeutic Class | Allogeneic cord blood hematopoietic progenitor cell therapy |
| Formulation | Cell suspension for infusion |
| Indication(s) | Hurler syndrome<br>Krabbe disease<br>X-linked adrenoleukodystrophy<br>Primary immunodeficiency diseases<br>Bone marrow failure<br>Beta thalassemia |
| Intended Population(s) | Adult and pediatric |

Template Version: March 6, 2009

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# Table of Abbreviations

| | |
|---|---|
| AAP | American Academy of Pediatrics |
| ALD | (X-linked) Adrenoleukodystrophy |
| AMN | Adrenomyeloneuropathy |
| BMF | Bone marrow failure |
| BMT | Bone marrow transplant |
| BRMAC | Biological Response Modifiers Advisory Committee |
| CI | Confidence interval (95%, unless otherwise specified) |
| CIBMTR | Center for International Blood and Marrow Transplant Research |
| COBLT | Cord Blood Transplantation (Study) |
| CTGTAC | Cell, Tissue, and Gene Therapies Advisory Committee |
| Docket | Collection of FDA dockets for cord blood |
| FA | Fanconi anemia |
| GVHD | Graft versus host disease |
| Hgb | Hemoglobin |
| HLA | Human leukocyte antigen |
| HPC-C | Hematopoietic progenitor cells – cord (umbilical cord blood) |
| HSCT | Hematopoietic stem cell transplant |
| IFAR | International Fanconi Anemia Register |
| IOM | Institute of Medicine |
| IST | Immunosuppressive therapy |
| IVIG | Intravenous immune globulin |
| MPS | Mucopolysaccharidosis |
| MRI | Magnetic resonance imaging |
| NMDP | National Marrow Donor Program |
| NYBC | New York Blood Center |
| PBSC | Peripheral blood stem cells |
| R-UCB | Related umbilical cord blood |
| SAA | Severe aplastic anemia (acquired) |
| SCID | Severe combined immunodeficiency |
| SD | Standard deviation |
| SE | Standard error |
| SEM | Standard error of the mean |
| TNC | Total nucleated cells |
| UCB | Umbilical cord blood (unrelated, unless otherwise specified) |
| U-UCB | Unrelated umbilical cord blood |
| VLCFAs | Very long chain fatty acids |

# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

### *Hurler Syndrome Indication*

This Reviewer recommends that UCB not be approved with an indication for Hurler syndrome on the grounds that there is lack of substantial evidence of efficacy.

Based on this Reviewer's assessment of the data available in the Docket and the literature, there is not substantial evidence that UCB has efficacy for improving survival in Hurler syndrome. The finding of enzyme elevation due to UCB is poorly documented and of uncertain clinical meaningfulness, and it is an insufficient basis for approval. There is lack of substantial evidence of an effect of UCB on other aspects of Hurler syndrome.

See Section 6, Efficacy Summary, Hurler Syndrome, for further discussion of the efficacy evidence.

### *Krabbe Disease Indication*

This Reviewer recommends that UCB not be approved with an indication for Krabbe disease on the grounds that there is lack of substantial evidence of efficacy.

Based on this Reviewer's assessment of the data available in the Docket and the literature, there is not substantial evidence that UCB has efficacy for improving survival in Krabbe disease. The finding of enzyme elevation due to UCB is poorly documented and of uncertain clinical meaningfulness, and it is an insufficient basis for approval. There is lack of substantial evidence of an effect of UCB on other aspects of Krabbe disease.

See Section 6, Efficacy Summary, Krabbe Disease, for further discussion of the efficacy evidence.

### *X-Linked Adrenoleukodystrophy Indication*

This Reviewer recommends that UCB not be approved with an indication for ALD on the grounds that there is lack of substantial evidence of efficacy.

Based on this Reviewer's assessment of the data available in the Docket and the literature, there is not substantial evidence that UCB has efficacy for improving survival in adrenoleukodystrophy (ALD). There is lack of substantial evidence of an effect of UCB on other aspects of ALD.

See Section 6, Efficacy Summary, Adrenoleukodystrophy, for further discussion of the efficacy evidence.

### *Primary Immunodeficiency Indication*

This Reviewer recommends that UCB be approved for improving survival in SCID. However, in this Reviewer's assessment, there is insufficient information to support a broad indication for all primary immunodeficiency diseases.

Based on this Reviewer's assessment of the data available in the Docket and the literature, substantial evidence has been provided that UCB has efficacy for improving survival in SCID, and the risks are acceptable. There was insufficient information in the Docket to evaluate evidence of efficacy for other primary immunodeficiency diseases.

See Section 6, Efficacy Summary, Primary Immunodeficiency Diseases, for further discussion of the efficacy evidence.

### *Bone Marrow Failure Indication*

This Reviewer recommends that UCB not be approved with an indication for bone marrow failure on the grounds that there is lack of substantial evidence of efficacy.

Based on this Reviewer's assessment of the data available in the Docket and the literature, there is not substantial evidence that UCB has efficacy for improving survival in Fanconi anemia (FA) or severe aplastic anemia (SAA). There is lack of substantial evidence of an effect of UCB on other aspects of these diseases. There was insufficient information in the Docket to evaluate the evidence of efficacy for other bone marrow failure conditions.

See Section 6, Efficacy Summary, Bone Marrow Failure, for further discussion of the efficacy evidence.

### *Beta Thalassemia Indication*

This Reviewer recommends that UCB not be approved with an indication for beta thalassemia on the grounds that the benefit-risk profile is not acceptable.

Based on this Reviewer's assessment of the data available in the Docket and the literature, substantial evidence has been provided that UCB can alter hemoglobin expression and make some patients transfusion independent. However, there is lack of substantial evidence that UCB has efficacy for improving survival in beta thalassemia, and, in fact, there appears to be an increased risk of mortality following UCB.

See Section 6, Efficacy Summary, Beta Thalassemia, for further discussion of the efficacy evidence.

## 1.2 Risk Benefit Assessment

### *Primary Immunodeficiency Indication*

Although some of the mortality following UCB for SCID is undoubtedly treatment related, underlying mortality due to disease is extremely high, and the risk is readily offset by much greater intermediate- and longer-term survival. Although patients with SCID due to adenosine deaminase (ADA) deficiency can be expected to benefit from UCB compared to *no* treatment, there remains a question about the acceptability of the risk of UCB in ADA-deficient SCID patients who are responsive to enzyme replacement therapy.

### *Beta Thalassemia Indication*

Although this Reviewer considers there to be substantial evidence for the efficacy of UCB in reversing transfusion dependence in beta thalassemia, the substantial mortality following UCB (see Section 6.7.4) is a significant concern that, in this Reviewer's assessment, makes the benefit-risk profile unacceptable, unless and until a subset of beta-thalassemic patients can be identified for whom additional benefit, such as improved longer-term survival, might be demonstrated to offset the acute risks, or for whom the treatment-related mortality could be substantially diminished.

# 2 Introduction and Regulatory Background

## 2.1 Product Information

This review is not for a specific product, but is applied to cord blood products as a whole (see also Product Comparability under Section 2.6). In general, HPC-C is a minimally manipulated placental/cord blood product containing live human cord blood cells for unrelated allogeneic use. The cord blood is collected for banking from newborns with maternal consent. It is cryopreserved for storage and shipping. The end user may dilute or wash the cells after thawing prior to intravenous administration.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

**Table 1: Available Treatments for Proposed Indications**

| Indication | FDA-Approved Therapies | Other Available Treatments |
|---|---|---|
| Hurler syndrome | Aldurazyme (laronidase) | HSCT |
| Krabbe disease | (none) | HSCT |
| Adrenoleukodystrophy | (none) | (b) (4) HSCT |
| Primary immunodeficiency diseases | IVIG (multiple brands)<br>Adagen (pegademase bovine) – for ADA-SCID | HSCT |
| Bone marrow failure | Atgam (antithymocyte globulin)<br>Actimmune (interferon γ) – for osteopetrosis | Thymoglobulin (antithymocyte globulin), Anadrol-50 (oxymethalone), Neupogen (filgrastim), cyclosporine, HSCT |
| Beta thalassemia | For iron overload: Desferal (deferoximine), Exjade (deferasirox) | RBC transfusion, HSCT |

## 2.3 Availability of Proposed Active Ingredient in the United States

UCB has been used in the US since sibling cord blood was used to treat a patient with Fanconi anemia in 1988, but as of the date of this review, no UCB product has been approved under a BLA. Although the FDA is embarking on a program to regulate these products and require that they be BLA-approved, the products have been available on the market through the FDA's exercise of enforcement discretion.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

On January 20, 1998, the FDA issued a notice in the Federal Register (63 FR 2985) titled *Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood Hematopoietic Stem/Progenitor Cell Products; Request*

*for Comments*. In this notice, the FDA requested the submission of proposals and data to support establishment controls, process controls, and product standards designed to ensure the safety and effectiveness of minimally manipulated unrelated allogeneic hematopoietic stem/progenitor cell products derived from peripheral and cord blood for hematopoietic reconstitution. Submitted comments were to include supporting clinical and nonclinical laboratory data and other relevant information. The comments and data received were placed in a public docket [Docket No. FDA-2006-D-0157] (formerly Docket No. 06D-0514). The initial comment period of two years (until January 20, 2000) was extended, at the request of industry, for 90 days until July 17, 2000 (65 FR 20825, April 18, 2000).

The Biological Response Modifiers Advisory Committee (BRMAC) was convened on February 27, 2003, to discuss issues related to the use of unrelated allogeneic hematopoietic stem/progenitor cells derived from placental/umbilical cord blood for hematopoietic reconstitution, including the analysis of clinical outcome data submitted to the public docket. On the basis of the assessment of submitted information, discussion of the BRMAC, and review of published literature on this subject, the FDA determined that the data were sufficient to provide recommendations for establishment and processing controls and product characteristics for these products and to establish the safety and effectiveness of HPC-Cs for allogeneic transplantation in the treatment of hematologic malignancies.

In 2007, the FDA announced the availability of *Draft Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies* dated December 2006 (Federal Register notice of January 17, 2007 (72 FR 1999)). A meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) was held on March 30, 2007, to discuss the draft guidance. The committee discussed access to HPC-Cs already in inventory and recommended additional clinical indications. In the process of finalizing the guidance, the FDA considered the recommendations of the CTGTAC, the public comments to the draft guidance, and additional data submissions.

The *Final Guidance for Industry: Minimally Manipulated Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications* was published on October 20, 2009 (74 FR 53753). The HPC-C licensure guidance provides recommendations to cord blood manufacturers applying for licensure of their HPC-Cs for the specified indications of hematologic malignancies, Hurler syndrome (MPS I), Krabbe disease (globoid leukodystrophy), X-linked adrenoleukodystrophy, primary immunodeficiency diseases, bone marrow failure, and beta thalassemia.

**Table 2: History of Development of Regulatory Policy for Cord Blood**

| | |
|---|---|
| 1997 | Human Cells, Tissues, and Cell- and Tissue-Based Products (HCT/P) Regulations Initiated |
| 1998 | FR notice: Request for Proposed Standards – Minimally manipulated unrelated allogeneic cord blood and PBSCs intended for hematopoietic reconstitution |
| 2003 | Convened Advisory Committee (BRMAC) on cord blood scientific issues |
| 2007 | Draft Guidance on BLA requirements published and comments gathered |
| 2007 | Advisory Committee (CTGTAC) convened |
| 2009 | Final BLA guidance and Draft IND guidance issued. FR notice announces intention to end enforcement discretion. |
| 2011 | INDs or BLAs required for distribution in US of allogeneic unrelated cord blood after October 20, 2011 |

A description of the prior human experience is available at www.regulations.gov under Docket numbers FDA-1997-N-0010 (Legacy Docket number 97N-0497) and FDA-2006-D-0157 (Legacy Docket number 06D-0514), which contain the data used to establish efficacy in the specified indications.

On October 20, 2009, the FDA announced through a Federal Register (FR) notice that it will end the period of phased-in implementation of IND and BLA requirements for minimally manipulated unrelated allogeneic placental/umbilical cord blood (HPC-C). The FR notice established a two-year implementation period, scheduled to end October 20, 2011, by which date all distribution of HPC-C for clinical use in the US must be done under an approved BLA or active IND.

## 2.6 Other Relevant Background Information

### *Background on Diseases*

Because of the numerous indications involved in the application, discussion of background for the various disease entities in this section would result in too fragmented a presentation. Therefore, background on each indicated disease is presented in the corresponding subsections of Section 6.

### *Product Comparability*

UCB is a product that has high variability inherent in the means by which it is produced. The cord blood guidance (FDA 2009) stipulated that any UCB product meeting the product characteristic requirements provided in that guidance is eligible to receive the indications it listed, without providing further data to support efficacy. In effect, all products satisfying those standards are regarded as “comparable” (in essence, pharmaceutically equivalent) to any (to-be-) marketed product approved under the conditions of that guidance.

However, related-donor bone marrow, unrelated-donor bone marrow, and peripheral blood stem cells have recognized differences from each other and from UCB regarding likelihood of engraftment, rates of engraftment, and incidence of various complications. None of these other products will be considered "comparable" to UCB in this review, and any substantial evidence of efficacy for those other products is not viewed as direct substantial evidence of efficacy for UCB.

### *Combination Therapy Issues*

For patients receiving UCB transplantation, with the exception of certain patients with primary immunodeficiency, a preparative regimen is required to avoid rejection of the hematopoietic graft. This may consist of radiation or combination chemotherapy. For the pediatric inborn error cases in the Duke dataset, for example, the vast majority received conditioning with busulfan, cyclophosphamide, and antithymocyte globulin. Conditioning regimens are not recorded in the other two datasets in the Docket.

For malignant diseases, the preparative regimen can reasonably be viewed as the primary therapy in which the objective is to eliminate a neoplastic cell line; the efficacy depends critically on how successfully this is achieved, and the hematopoietic stem cell therapy (HSCT) plays more of the role of "rescue" therapy, although it is also replacing hematopoietic functions that have been affected by the disease, and a "graft vs. leukemia" effect may play a role in efficacy. For the nonmalignant proposed indications, the HSCT can be viewed as the primary therapy, because the objective is to provide a hematopoietic function that is absent or seriously deficient due, in most cases, to an inborn disease (acquired bone marrow failure being an exception). Efficacy is derived directly from the ability of the HSCT to provide those functions, but success is still importantly influenced by the effectiveness of the preparative regimen in facilitating engraftment.

Use as a preparative regimen for HSCT is an approved indication for IV busulfan (Busulfex), used in conjunction with cyclophosphamide, only for treatment of CML. Labeling for cyclophosphamide does not explicitly describe its use for HSCT. Although the Busulfex labeling described one preparative regimen, others have been used. For some conditions, notably Fanconi anemia, reduced-intensity regimens are recommended. The regulatory status of the conditioning regimens should be kept in mind for the review and the regulatory action for UCB products. Ideally, an assessment of the effectiveness of UCB transplantation should take the preparative aspect of the combined therapy into account, but the necessary information is not available. A full evaluation of the safety and efficacy of the drug products or devices used in the preparatory regimens for the various indications is beyond the scope of this review. Any regulatory action regarding the current application should be taken with an awareness of potential implications regarding explicit or implicit approval of off-label uses for the agents used in preparatory regimens.

# 3 Ethics and Good Clinical Practices

The material being reviewed in support of efficacy for a cord blood BLA is primarily the material that was submitted to the three separate FDA dockets associated with regulation of allogeneic cord blood cell transplantation, supplemented with data from publications. The information submitted to the dockets from those outside the FDA was provided voluntarily in response to public solicitations by the FDA, and there was no requirement that docket submissions be limited to information that was collected under an IND or that would meet standards expected for a BLA application. Consequently, the information submitted to the dockets is accepted "as is."

Deficiencies in the submitted data are described below. It is important to identify the deficiencies for purposes of understanding the limitations that apply to conclusions that might be drawn from the data. However, because submitters were not subject to BLA requirements, deficiencies cannot be viewed as having implications regarding regulatory integrity or as calling for any official corrective action relating to the submitters.

## 3.1 Submission Quality and Integrity

### *Organization*

This review is for the non-malignant indications for cord blood that are listed in the Cord Blood Guidance (FDA 2009), and is intended to be applicable to any BLA that restricts requested indications to those listed in that Guidance, that references the dockets in support of those indications, and that presents no other evidence and analysis in substantiation of efficacy. The material submitted to the dockets was a series of documents with no meaningful indexing or overarching organization. Because this review is without reference to a specific BLA, and rests only on submissions to the dockets and on published literature, there was no Integrated Summary of Efficacy, Reviewer's Guide, complete study reports, or other materials provided to assist in organizing the efficacy data and to provide argument as the adequacy of the efficacy data to support approval.

### *Dataset Quality and Integrity*

See Section 5.1 for a description of the relevant docket documents. The following discussion applies to the three datasets that were regarded as the primary sources of clinical data (Tier 1 datasets).

#### Common Issues

*Incompleteness*

All three datasets lack information on diagnostic criteria that were used, patient status (although cancer stage was provided by the NMDP and NYBC datasets, and Lansky score was provided in the Duke dataset); there are no laboratory data, imaging results,

or genotyping data. Only the Duke dataset included information on the preparative regimen used. All three datasets included outcome information consisting of engraftment information, complications (such as GVHD), and mortality, but no disease-specific outcomes such as transfusion independence, immunologic testing, infection frequency, hemoglobin type, extent of chimerism, physical exam findings, or neurologic evaluation (although enzyme values were provided in the Duke dataset).

*Lack of Case Report Forms*
None of the datasets is accompanied by case report forms for deaths and discontinuations.

*Possible Duplicate Reporting*
The Duke dataset is the report of the experience at a single treating institution, and the cord blood units used came from banks at other sites, with a substantial number coming from the NYBC and through the NMDP. Although the source of the unit was identified in the Duke dataset, there is insufficient information in each of the datasets to identify clearly whether or not a patient may have information reported in more than one of these datasets. Concordance of ages and survival times for certain patients suggests, but does not establish, that there may be duplicate reporting in at least a few cases. See Section 5.2 for the strategy used to reduce duplication.

*Lack of Data Standards*
The datasets did not comply with SDTM standards nor did they employ common coding or variable names, so that pooled analyses required additional manipulation of the datasets in most cases, and was not feasible for some other types of data.

## Issues with the NMDP Dataset

The NMDP dataset lacked information on prefreeze viability of the units for 81% of patients. Two infants had cause of death listed as “RECUR/RESDL LEUK,” although one had Krabbe disease and one had another inborn error of metabolism; this raises questions about either the primary disease categorization or the accuracy of the reporting of reasons for death.

## Issues with the NYBC Dataset

The NYBC dataset lacked information on gender, race, and product attributes. Age is only given as an integer, even for patients under 1 year of age.

## Issues with the Duke Datasets

The Duke datasets had no data definition file; however, the meaning of most variables could be inferred from the variable names.

This Reviewer easily identified isolated errors (such as gender of "N" when all others were "F" or "M" (pt (b) (6)) or a value of 19 on a scale of 0 to 10 (pt (b) (6))). In the electronic dataset that accompanied the docket submission, the date of transplant appears three times but was inconsistent for one patient (pt (b) (6)). Patient numbers were not consecutive, raising a question of selection bias, although the missing numbers might correspond to BMT patients. A separate dataset for enzyme data (which also includes BMT patients) was provided in printout form (docket document 2006-D-0157-DRAFT-0054) but without patient numbers to permit cross-linking to the main Duke dataset. However, matching by transplant date did allow a presumptive correspondence. Using that correspondence, it was noted that patient (b) (6) was coded as Hurler syndrome in the main dataset, but the one patient with the same transplant date was coded as Hunter syndrome in the enzyme dataset. It appears that even basic range and value validation checks were not performed for the Duke dataset, and it is reasonable to question the accuracy of these data in general.

*Significant data quality problems were identified in the Duke dataset:*

1) For the reported follow-up times, the value listed for overall survival days for those patients who had not died was provided – not as a specific value – but as an Excel spreadsheet function reporting the number of days between the transplant date and the current date (i.e., the date on which the spreadsheet was being viewed). In comparing the electronic dataset to the printout of the dataset in the dockets, the survival times could be made to agree by substituting 4/17/2007, the date that appears on the docket printout, for the current date function in the Excel spreadsheet. Further, patient (b) (6) diagnosed with ALD, has a cause of death listed, but is not treated as having died for purposes of reporting a survival time. Thus, it appears that the survival times did not represent a recorded date on which the patients were known to be alive. Rather, it appears as though any patients not listed as having died were treated as if still alive as of the date of the printout. The survival times listed in that dataset therefore cannot be considered a reliable representation of known follow-up times for patients who are not listed as dead.

2) Review of the literature uncovered a report of a patient with beta thalassemia who received UCB transplantation at Duke in 1998 (Hall and Martin et al. 2004). No patient with a diagnosis of beta thalassemia was found in the Duke dataset. Further, review of the literature uncovered an article reporting on the Duke experience in which a patient with ALD died after beginning the conditioning regimen but before receiving a transplant (Beam and Poe et al. 2007). There is sufficient information in the article to determine that the patient was not included in the Duke dataset. The Duke dataset cannot be considered a complete record of patients who began the process of cord blood transplantation at that site, and not all deaths after starting treatment have been reported.

## 3.2 Compliance with Good Clinical Practices

Good Clinical Practice (GCP) compliance cannot be evaluated from the data and datasets submitted to the dockets. Although the dataset from the NMDP was represented as being collected under IND 7555, no protocol, informed consent forms, or related materials were submitted to the dockets for the NMDP dataset, or for either of the other two datasets. In some cases, e.g., the Duke dataset, accompanying information in the dockets gives some information about how data were collected, but the details that would typically be provided for a prospective study are lacking. For other documents that provided only summary results, no information is provided to address compliance with GCP.

Because the data were provided to the dockets apart from any BLA submission by parties not acting in the role of a BLA applicant, no clinical site inspections were requested.

## 3.3 Financial Disclosures

No financial disclosures were provided for the Docket documents.

# 5 Sources of Clinical Data

"The Docket"

The material being reviewed in support of efficacy for a cord blood BLA is primarily the material that was submitted to the three separate FDA dockets associated with regulation of allogeneic cord blood cell transplantation: Dockets FDA-1997-N-0010 (Legacy Docket number 97N-0497), FDA-2006-D-0157 (Legacy Docket number 06D-0514), and FDA-2009-D-0490). This collection of dockets will be referred to simply as "the Docket" in this review. Information in addition to those three datasets was also considered in the review. The Docket submissions of potential relevance are described in Section 5.1.

Literature

This Reviewer searched the literature for publications not provided in the Docket in an effort to identify appropriate external (historical) control data for comparing to the UCB experience reported in the Docket and to identify other publicly available information about experience with cord blood transplantation for the candidate indications. Data from publications that were only available online (such as publications from CIBMTR.org that were not available in a journal publication) were not relied upon as sources of data for this review.

Additional details of the literature search strategy, along with the cited references, are given in Section 9.1.

## 5.1 Tables of Studies/Clinical Trials

The Docket included numerous submissions that did not provide clinical data, and those were not considered further for this review. The documents that did contain clinical data are itemized below. The Docket did not provide any indexing or organization that was relevant to an efficacy review. Therefore, this Section provides a structured listing of the clinical data in the Docket. To further organize the submission, this Reviewer categorized the documents into Tiers, reflecting perceived relevance to the evaluation of the efficacy of UCB.

Tier 1: Detailed data on UCB transplantation

1. NMDP Dataset
   - Patient listings of 581 patients who received a single unit from Feb 2000 through Dec 2006. Includes data on recipient, product, and outcomes (survival, engraftment, GVHD).

- Excel dataset is provided in Docket document 1997-N-0010-0032. Excel spreadsheet of summary tabulation for each variable (1997-N-0010-0033) is serviceable as a data definition document.

- An analysis of 1-year survival and predictive factors for a subset of 548 patients, not broken down by disease, is provided in 1997-N-0010-0016, and summary and printout of cord blood transplants from Feb 2000 to Dec 2005 collected under IND 7555 (n=353) are provided in 1997-N-0010-0019, and -0021.

2. NYBC Dataset
   - Patient listing of 562 consecutive patients given cord blood from the NYBC program. These patients are the same as those reported by Rubinstein (Rubinstein and Carrier et al. 1998) but updated through May 2001 and with some corrections. The dataset provides limited patient demographics and only a little information on the attributes of the product infused.

   - It is provided as summary tables for the variables and as a printed tabulation spanning two docket documents (1997-N-0010-DRAFT-0042, and -0043). The variable summaries are serviceable as a data definitions document. An electronic dataset was described in the cover letter and made available to FDA, but it is not present as a docket document. On spot-checking, the electronic dataset appears to correspond to the printout in the docket.

3. Duke Datasets
   - Patient listings of 160 patients given UCB transplants at Duke University, primarily for pediatric inborn errors of metabolism. A separate dataset provides pre- and post-transplant enzyme levels on a subset of these patients and for some BMT patients.

   - Docket document 2006-D-0157-DRAFT-0055 is a printout of the main dataset. An electronic dataset was described in a related docket document and was made available to the FDA, but was not present as a docket document. The electronic dataset appears to correspond to the docket printout, with a notable exception regarding follow-up times as discussed under Section 3.1. There is no data definitions document.

   - Document 2006-D-0157-DRAFT-0054 (and also -0082) contains the printout of the pre- and post-transplant enzyme values. There is no accompanying data definitions document. No electronic dataset was located by this Reviewer, but one was created by pasting from the printout into an Excel spreadsheet.

   - Documents 2006-D-0157-DRAFT-0044, -0045, -0046, -0052, -0082 contain Duke report, tables, and graphs regarding factors affecting survival and engraftment in

158 pediatric patients (apparently the first 158 patients in the Duke dataset). The report presents summary data that are not disease-specific, but some of the affiliated tables and graphs show results by disease.

4. (b) (4) Case Reports
   - 2006-D-0157-DRAFT-0078 is a publication (Jaing and Lee et al. 2006) of a case report of UCB transplantation in a patient with SCID.
   - 2006-D-0157-DRAFT-0079 is a draft article on a case series of five UCB transplants for beta thalassemia.
   - 2006-D-0157-DRAFT-0080 is a publication (Jaing and Hung et al. 2005b) of a single case report of UCB transplantation for beta thalassemia in Taiwan. (This patient is also included in the case series.)
   - 2006-D-0157-DRAFT-0081 is a publication (Jaing and Hung et al. 2005a) of a case series of five UCB transplants for beta thalassemia. It closely resembles the draft case series article above (-0079), but there are some minor differences.

<u>Tier 2: Less detailed data regarding UCB transplantation</u>

5. 1997-N-0010-DRAFT-0021: Analysis by (b) (4) on transient warming and viability, with reference to a publication (Rubinstein and Carrier et al. 1998) on general factors affecting engraftment of UCB and event-free survival. The publication does not provide much detail on death alone. Analyses are not broken down by disease.

6. 1997-N-0010-DRAFT-0034: St. Louis Cord Blood Bank analysis of effect of storage time on engraftment and survival; analyses are not broken down by disease.

7. 1997-N-0010-DRAFT-0035, -0037: NYBC analyses of factors affecting engraftment speed, transplant-related events, and leukemic relapse. This is based on an experience in 1019 patients, and so is not the same as the dataset in item 2, above.

8. 1997-N-0010-DRAFT-0039: Univ. of Minnesota analysis of factors affecting engraftment, GVHD, and 2- and 4-year survival.

9. 1997-N-0010-DRAFT-0062, -0063: (b) (6) PowerPoint slides on effects of TNC and CD34+ counts on engraftment and survival.

10. 2006-D-0157-0007: CIBMTR summary tabulations regarding 42-day engraftment and 1- and 2-year survival for non-malignant conditions. Some analyses were done by specific disease.

11. 2006-D-0157-DRAFT-0064, -0065: NYBC analysis of engraftment and survival to 1 year from single UCB transplant by broad disease categories. This is based on experience in 1,618 patients, and so is not the same as either item 2 or item 7, above.

12. 2006-D-0157-DRAFT-0069, -0070, -0072, -0077: (b) (4) -submitted publication (Chow and Nademanee et al. 2007) on factors affecting UCB transplant engraftment and survival in 283 patients. First two documents are drafts that contain some tables not included in published version (last two documents).

Tier 3: Detailed data regarding HSCT other than UCB

13. NMDP data on 1178 peripheral blood stem cell (PBSC) transplants
    1997-N-0010-0018, -0020, -0023, -0029: data dictionary
    1997-N-0010-0022: printed dataset of PBSC cases # 1-1178
    1997-N-0010-0024, -0025, -0026, -0027, -0030, -0031: Excel datasets
    1997-N-0010-0028: report
    1997-N-0010-DRAFT-0073, -0074, -0075, -0078, -0080: dataset printouts

Tier 4: Less detailed data regarding HSCT other than UCB

14. 1997-N-0010-DRAFT-0105, -0015: NMDP-submitted publication (van Rood and Oudshoorn 2008) of a special report on BMT that presents an analysis of factors affecting survival.

## 5.2 Review Strategy

### *Scope of the Review*

This review is limited to an evaluation of the evidence supporting efficacy of those indications listed in the guidance for cord blood (FDA 2009). This review is not intended to include a review of safety; safety data from the Docket are addressed in a separate Docket safety review.

### *Scope of Diseases Considered*

This efficacy review is an evaluation of the evidence supporting efficacy for those non-malignant indications listed in the guidance for cord blood (FDA 2009). Some of those indications identified specific diseases (Hurler syndrome, Krabbe disease, adrenoleukodystrophy, and beta thalassemia), whereas others identified broad categories of disease that could include numerous different conditions as candidate indications (primary immunodeficiency and bone marrow failure). For the latter groups of indications, the review efforts were directed towards those conditions that were substantially represented in the data submitted to the docket.

For the primary immunodeficiency diseases, the datasets submitted to the Docket contained the numbers of cases shown in Table 3.

**Table 3: Immunodeficiency Diseases Represented in Docket Datasets**

| Disease | Cases in Datasets |
|---|---|
| SCID | 47 |
| Wiskott-Aldrich Syndrome | 14 |
| Kostmann disease | 4 |
| Lymphocyte adhesion disorder | 4 |
| Chronic granulomatous disease | 3 |
| Chediak Higashi syndrome | 2 |
| Combined immunodeficiency (not SCID) | 1 |
| Common variable immunodeficiency | 1 |
| Nezelof syndrome | 1 |
| Other/unknown | 4 |

Consequently, the review for primary immunodeficiency focused on SCID. The other diseases were considered to be too sparsely represented in the Docket datasets or in any of the other submissions to the Docket to have a reasonable prospect of generating substantial evidence of efficacy.

For bone marrow failure diseases, the datasets submitted to the Docket contained the conditions listed in Table 4. (While osteopetrosis might be categorized as an inborn error of metabolism, it was included in this listing because bone marrow failure is a significant aspect of the disease.)

**Table 4: Bone Marrow Failure Diseases Represented in Docket Datasets**

| Disease | Cases in Dataset |
|---|---|
| Fanconi anemia | 39 |
| Severe aplastic anemia | 37 |
| Osteopetrosis | 16 |
| Amegakaryocytic thrombocytopenia | 4 |
| Diamond-Blackfan anemia | 4 |
| Dyskeratosis congenita | 2 |
| Shwachman-Diamond syndrome | 1 |

The review for bone marrow failure diseases focused on Fanconi anemia and severe aplastic anemia. The other conditions listed were considered to be too sparsely represented in the Docket datasets or in any of the other submissions to the Docket to have a reasonable prospect of generating substantial evidence of efficacy.

### *Scope of Materials Reviewed*

For the material submitted to the Docket, the main focus of the review was on the materials identified as Tier 1 data in Section 5.1, which are the datasets that contained individual patient data from patients who had received UCB and significant case reports. Summary information on patients who had received UCB (Tier 2 data) was also

considered, but, due to its nature, was not subjected to extensive analysis. Datasets and other types of information regarding HSCT other than UCB (Tier 3 and 4 data) were not subjected to detailed review.

Material outside the Docket that was reviewed in detail consisted of published reports of natural disease history for the diseases under consideration, as well as any reports of investigations or other significant clinical experience using UCB for those diseases.

### *Pooling/Duplicates*

Since the numbers of patients for the non-malignant indications were generally rather small, and because any control groups were external to those datasets anyway, the three major UCB datasets were pooled to improve precision of estimates of survival for the non-malignant indications. It is possible that this approach may result in counting some patients twice, because duplicate reporting between Duke, which is a transplant center, and the other two dataset submitters, which are cord blood providers, cannot be ruled out (see Section 3.1). The datasets were inspected visually to identify cases with identical or nearly identical attributes, including transplant date, demographics, product attributes, and survival time. The following presumptive duplicates were identified, and the duplicates were eliminated for purposes of the efficacy analyses:

**Table 5: Presumptive Duplicate Cases**

| Duke Pt # | Diagnosis | Other Record | |
|---|---|---|---|
| (b) (6) | Hurler | NYBC | (b) (6) |
| | Hurler | NYBC | |
| | Hurler | NYBC | |
| | Hurler | NYBC | |
| | Hurler | NMDP | |
| | Hurler | NMDP | |
| | Hurler | NMDP | |
| | Hurler | NMDP | |
| | | | |
| | Krabbe | NYBC | |
| | Krabbe | NMDP | |
| | | | |
| | ALD | NYBC | |
| | ALD | NMDP | |

### *Controls*

The data provided in the Docket reflected essentially only uncontrolled experience with UCB transplantation. To meet the regulatory requirement to base approval on well controlled investigations, this Reviewer searched the literature for historical data in an attempt to identify appropriate control populations. See Section 9.1 regarding search strategy, and the control data presented in subsections of Section 6. The FDA ICH E10 document (FDA 2001) discusses considerations pertaining to selection and quality of external control data. Other discussion on the limitations of historical controls and database evaluation to assess efficacy can be found in Temple 1990.

### *Selection of Endpoints*

The principal clinical efficacy outcome provided by the three major Docket datasets was time to death, and there was little additional information to help assess clinical effectiveness. Consequently, the primary efficacy endpoint for most of the nonmalignant indications was taken to be time until death. Death is an objective outcome that has the advantage in historically controlled comparisons of being readily interpretable across studies. Time to death also is relevant for most of the proposed indications, because most involve significantly increased mortality. Time to death is nonetheless subject to weaknesses relating to completeness of follow-up and reasons for loss to follow-up; the latter can be difficult to assess for both the docket data and historical control data.

While there are other aspects of response to therapy that would be clinically meaningful for the various diseases, their assessment was not, with a few exceptions, accommodated by the information in the docket datasets. For Hurler syndrome and Krabbe disease, information on pre- and post-transplant enzyme levels was provided, although with no additional documentation of clinical status. Enzyme levels are of uncertain clinical meaningfulness, and were viewed as secondary endpoints

For the indications in which there are well documented case reports, there was an opportunity to try to assess additional outcomes. The two conditions for which such reports were provided were SCID and beta thalassemia. For SCID, the case report documents freedom from infection and significantly improved immune function in addition to improved survival. For beta thalassemia, case series provide information on elimination of transfusion dependence, and hemoglobin electrophoresis results are provided for one of these cases.

For all indications, additional outcome data were available concerning proportions of patients achieving engraftment and times to engraftment for neutrophils and platelets. While these might be regarded as reflecting an aspect of effectiveness, engraftment factors are addressed in a separate Clinical Safety Review, because delayed or failed engraftment presents significant risks to the patient.

### *General Organization of the Efficacy Review and Modifications to the Review Template*

To help keep information unified in the face of the numerous indications under consideration, all discussion of clinical trials is located in subsections of Section 6, rather than under Section 5.3. For the indication of bone marrow failure, for which the two specific entities of Fanconi anemia and severe aplastic anemia are considered, each condition is given its own complete major subsection. Within each indication under Section 6, baseline treatment data are included under Demographics. The subsections 6.X.6 on Other Endpoints are omitted, as there are no additional experimental or exploratory endpoints for any of the indications. Also, subsections 6.X.9 on Discussion of Persistence of Efficacy and/or Tolerance Effects are omitted.

Section 4 is omitted as not relevant, because this review is for Docket efficacy data and not a specific BLA. Sections 7 and 8 were omitted because the Docket safety data are addressed in a separate safety review. Sections 9.2 and 9.3 are omitted because the review is not for a specific BLA.

## 5.3 Discussion of Individual Studies/Clinical Trials

See the discussions for each indication in the subsections of Section 6.

# 6 Review of Efficacy

## ***Efficacy Summary***

### *Hurler Syndrome*

The Docket datasets provided information on survival following UCB transplant for Hurler syndrome, but did not provide any control data for comparison. One reasonable candidate for an historical control was identified from the literature. Based on the data submitted to the Docket, there is early mortality with UCB transplantation in Hurler syndrome, with a break-even point that appears to occur somewhere between 5 and 9 years after transplant, compared to historical controls. However, the follow-up data in the Docket datasets are very sparse at 9 years. In addition, there is an inability to evaluate the comparability of Docket patients and historical controls due to limited individual patient data for both Docket and historical control patients regarding baseline attributes and concurrent therapy. Further, the Docket dataset that provides the majority of the evidence for this disease (Duke dataset) has data quality issues regarding length of follow-up that make the conclusions from those data unreliable. Therefore, in this Reviewer's assessment, the available data do not provide substantial evidence that UCB transplant improves survival in Hurler syndrome.

Although the survival curve for UCB appears very similar to that for bone marrow transplant in Hurler syndrome, the similarity is clearest only for the period that includes the high early mortality, but the small numbers of UCB patients followed for at least a decade means there is little evidence by which to judge the similarity to BMT in that extended time frame.

Changes in enzyme levels were reported in the Docket, but the data were not well documented, and the clinical meaningfulness of an elimination of blood enzyme levels is unclear. No other clinical outcome data were provided in the Docket datasets. Evidence from published data regarding the effect of UCB on other aspects of Hurler syndrome is limited by the lack of objective comparisons to controls and by susceptibility to possible selection or reporting bias.

No clear relationship was seen between UCB dose and survival in Hurler syndrome over the range of doses used in the Docket dataset.

### *Krabbe Disease*

The Docket datasets provided information on survival following UCB transplant for Krabbe disease, but did not provide any control data for comparison. One reasonable source of historical control data was identified from the literature. Based on the data submitted to the docket, the overall survival experience following UCB for Krabbe disease appears to overlap that of candidate historical controls; variability of the

phenotype and uncertainty about the phenotypes of patients in the Docket datasets make control selection challenging. There is an inability to evaluate the comparability of Docket patients and historical controls due to limited individual patient data for both Docket and historical control patients regarding baseline attributes and concurrent therapy. Further, the Docket dataset that provides the majority of the evidence for this disease (Duke dataset) has data quality issues regarding length of follow-up that make the conclusions from those data unreliable. The literature seems to indicate no benefit from UCB transplant in Krabbe disease once symptoms develop, but suggests that presymptomatic transplantation is effective in improving survival. Interpretation of the evidence for the latter conclusion is limited by difficulty in determining phenotype prior to symptom onset, uncertainty about the comparability of the UCB and control groups, and the apparently post hoc nature of the subgroup analysis. Also, more recent observations suggest that UCB-transplanted patients with Krabbe disease are still severely affected. Therefore, in this Reviewer's assessment, the available data do not provide substantial evidence that UCB transplant improves survival in Krabbe disease.

Changes in enzyme levels were reported in the Docket, but the data were not well documented, and the clinical meaningfulness of an elimination of blood enzyme levels is unclear. No other clinical outcome data were provided in the Docket datasets. Evidence from published data regarding the effect of UCB on other aspects of Krabbe disease is limited by lack of objective comparisons to controls and by susceptibility to possible selection or reporting bias.

No clear relationship between UCB dose and survival in Krabbe disease was observed over the range of doses used in the Docket dataset.

### *X-Linked Adrenoleukodystrophy (ALD)*

The Docket datasets provided information on survival following UCB transplant for ALD, but did not provide any control data for comparison. A small number of candidate historical control groups were identified from the literature. The phenotype in ALD is variable, and, without knowledge of the age at onset of symptoms and the degree of MRI abnormalities in the study population, it is difficult to assess the prognosis of the patients who were transplanted and to identify an appropriate historical control. While there is some suggestion that overall survival following UCB transplantation for ALD patients in the Docket database is better than that of untransplanted patients who have had onset of neurologic symptoms, it appears to be worse than survival in diagnosed untransplanted patients who have not developed MRI abnormalities. Overall, based on the data submitted to the Docket, the survival experience following UCB for ALD appears to overlap that of candidate historical controls, including the most recent available natural history experience. There is an inability to evaluate the comparability of Docket patients and historical controls due to limited individual patient data for both Docket and historical control patients regarding baseline attributes and concurrent therapy. Further, the Docket dataset that provides the majority of the evidence for this disease (Duke dataset) has data quality issues regarding length of follow-up that make

the conclusions from those data unreliable. In a report of an epidemiologic study suggesting better outcomes with HSCT vs. No HSCT in ALD, the Docket survival experience more closely resembled the No HSCT group. Therefore, in this Reviewer's assessment, the available data do not provide substantial evidence that UCB transplant improves survival in ALD.

No clinical outcome data other than survival were provided in the Docket datasets. Evidence from published data regarding the effect of UCB on aspects of ALD other than survival is limited by lack of objective comparisons to controls and susceptibility to possible selection or reporting bias.

No clear relationship between UCB dose and survival in ALD was observed over the range of doses used in the Docket dataset.

### *Primary Immunodeficiency*

Primary immunodeficiency covers a heterogeneous group of diseases. Only severe combined immunodeficiency (SCID) was considered to be represented in the Docket in sufficient numbers to have a reasonable prospect of providing sufficient data to support efficacy. Therefore, only SCID was reviewed for this indication group.

#### Severe Combined Immunodeficiency (SCID)

The Docket datasets provided information on survival following UCB transplant for SCID, but did not provide any control data for comparison. Two sources of candidate historical control data were identified from the literature. The approximately 2/3 survival for several years following UCB for SCID is in striking contrast to the near uniform early fatality in SCID seen in two historical control groups. The Docket data and historical control data are limited in the ability to evaluate comparability of the treated and control populations because of the limited information regarding baseline characteristics and concurrent therapy. The presence of some patients older than 2 years raises some questions about the diagnostic criteria or the relevance of the historical controls. However, the apparent effect remained statistically and clinically striking when subjected to various sensitivity analyses. In light of the dramatic size of the treatment effect on an objective and clinically significant endpoint, this Reviewer feels that the comparisons of the Docket data to the historical data can be regarded as an adequately controlled clinical investigation.

A single reasonably detailed case report from the literature (that was also submitted to the Docket) provided evidence of prolonged survival and improved immune status in a SCID patient compared with the known natural history of the disease.

Therefore, in this Reviewer's assessment, the available data provide substantial evidence in the form of a controlled investigation, with supporting information provided by a detailed case report, that UCB transplant improves survival in SCID.

No clear relationship was seen between cell dose and survival over the range of doses used.

### *Bone Marrow Failure*

Bone marrow failure covers a heterogeneous group of diseases. Only Fanconi anemia (FA) and severe aplastic anemia (SAA) were considered to be represented in the Docket in sufficient numbers to have a reasonable prospect of providing sufficient data to support efficacy. Therefore, only FA and SAA were reviewed for this indication group. Each is presented separately below:

#### Fanconi anemia (FA)

The Docket datasets provided information on survival following UCB transplant for FA, but did not provide any control data for comparison. One source of historical data was identified, but its ability to provide an appropriate control group was limited. Based on the data submitted to the Docket, the 72% one-year mortality following UCB transplant in FA well exceeds the mortality in the general FA population, and there is little UCB follow-up beyond 2 years. Although the UCB-transplanted FA patients undoubtedly reflect a select subgroup of FA regarding prognosis, prognosis could not be evaluated from the docket data. A published epidemiologic analysis of the historical data suggested HSCT (not necessarily UCB) was associated with a 5-fold increased hazard for mortality in the subset of FA patients with who had had onset of hematologic features of the disease, but the observational nature of study limits its interpretability. Published literature in Fanconi anemia generally confirms a similarly high mortality following UCB transplant. Based on the data available, no evidence was identified that demonstrates a survival benefit for UCB transplant in FA. Therefore, in this Reviewer's assessment, the available data do not provide substantial evidence that UCB transplant improves survival in FA.

No clinical outcome data other than survival were provided in the Docket datasets.

From analysis of the docket datasets, survival appeared to be related to TNC dose, with patients who received a dose $< 2.5 \times 10^7$ TNC/kg experiencing noticeably worse survival, although those with doses above that level did not fare substantially better than the group as a whole. Due to the high treatment-related mortality inherent in the conditioning regimen that is an intrinsic part of UCB therapy in this disease, the finding of a dose response cannot be regarded as sufficient to demonstrate evidence of efficacy in this situation.

Severe aplastic anemia

The Docket datasets provided information on survival following UCB transplant for FA, but did not provide any control data for comparison. Several candidate historical control groups were found, but there was variation in reported survival rates. There is an inability to evaluate the comparability of Docket patients and the various historical controls due to limited individual patient data for both Docket and historical control patients regarding baseline attributes and concurrent therapy. Based on the limited data submitted to the docket, the overall survival experience appears to overlap that seen in older control data, and tends to be lower than survival proportions seen in more recent control experience, including cohorts of patients unresponsive to immunosuppressive therapy. The evidence from the published literature regarding the effect of UCB on survival or other effects in SAA is limited by the lack of controls and possible selection or reporting bias. A recent published report of survival experience following UCB for SAA from a large series is not appreciably different from the survival experience observed in the Docket data. The authors of that report recommended that prospective studies are needed before UCB can be recommended for SAA. Therefore, in this Reviewer's assessment, the available data do not provide substantial evidence that UCB transplant improves survival in SAA.

No clinical outcome data other than survival were provided in the Docket datasets.

From an analysis of the Docket datasets, survival appeared to be related to TNC dose, with patients who received a dose $< 2.5 \times 10^7$ TNC/kg experiencing worse survival, although those with doses above that level did not fare substantially better than the group as a whole. Due to the high treatment-related mortality inherent in the conditioning regimen that is an intrinsic part of UCB therapy in this disease, the finding of a dose response cannot be regarded as sufficient to demonstrate evidence of efficacy in this situation.

### *Beta Thalassemia*

The Docket datasets provided only very limited data (n=8) on survival following UCB transplant for beta thalassemia, and they did not provide any control data for comparison. Search of the literature identified only a few candidate historical groups and a few substantial reports of experience with UCB in beta thalassemia. Therefore, the ability to evaluate the comparability of UCB treated groups and historical controls was limited. The evidence from published literature regarding the effect of UCB on survival showed a range of results, but outcomes appeared to be unfavorable compared to the expected usually excellent short- to intermediate-term prognosis for pediatric patients with beta thalassemia. A recent review reported outcomes with UCB that appeared to be worse than those with other forms of HSCT, leading the authors to conclude that the use of UCB for beta thalassemia was "suboptimal" for hemoglobinopathies and discouraged its use outside of well-designed clinical trials.

Published series generally report the ability of UCB to eliminate transfusion dependence, although that endpoint is not explicitly defined. Reasonably detailed case reports in the literature also document the ability of UCB to eliminate transfusion dependence and to improve the hemoglobin profile toward normal.

In this Reviewer's assessment, there is substantial evidence of the ability of UCB to improve the hemoglobinopathy and alleviate transfusion dependence in beta thalassemia major. However, the survival experience following UCB appears to be worse than any available historical controls, which brings into question the benefit-risk profile.

## 6.1 Hurler Syndrome

Mucopolysaccharidosis I (MPS I) is a lysosomal storage disorder caused by deficiency of alpha-L-iduronidase (IDUA). It is autosomal recessive and caused by a mutation of the gene for IDUA located on chromosome 4p16.3. Incidence is estimated at 1 per 100,000 live births (Muenzer and Wraith et al. 2009). Diagnosis is made by enzyme assay of alpha-L-iduronidase in leukocytes or cultured fibroblasts. Molecular diagnosis is complicated by genetic heterogeneity. The phenotype is variable, and MPS I is subclassified as Hurler syndrome (MPS I-H) for the most severe cases, Hurler-Scheie (MPS I-HS) for moderate cases, and Scheie (MPS I-S) for the mildest cases. The classification is based on clinical presentation. About 50% to 80% of MPS I cases are Hurler syndrome.

The classical features of Hurler syndrome are coarse facial features, corneal clouding, mental retardation, hernias, skeletal and joint abnormalities, and hepatosplenomegaly (Neufeld and Muenzer 2001). Diagnosis is usually made in the first year of life. Untreated, average age at death is generally reported as 5 years, and survival beyond 10 years is uncommon. Aldurazyme (laronidase) is an approved enzyme replacement therapy for the disease.

Hurler-Scheie syndrome differs from Hurler syndrome in that the former usually is diagnosed between two and six years of age, has less coarse facial features, often includes a small mandible, and features toe walking due to Achilles tendon contractures. The condition progresses less rapidly, usually does not involve mental retardation, and patients usually survive into their twenties. Scheie syndrome is milder and lifespan is longer. Diagnosis of Scheie syndrome may be delayed until teenage years, and presenting symptoms are usually joint stiffness and corneal clouding.

### 6.1.1 Methods

Efficacy was evaluated by computing estimates for post-transplant survival obtained from pooling the three datasets described in Section 5.1. Results were compared to historical control survival data obtained from the literature. The literature was reviewed for additional reports of experience with unrelated cord blood use for Hurler syndrome.

Diagnostic information other than the diagnosis of Hurler syndrome was not provided. Thus, eligibility criteria for the series and the criteria for classification of the phenotype are unknown. Most (67%) of the cases came from the Duke dataset, in which diagnosis of Hurler-Scheie also appeared, indicating that a distinction between the two was made in that dataset. Apart from post-transplant enzyme levels, information on disease-specific outcomes that might have been of interest, such as mental ability, physical ability, or organomegaly, were not provided. As noted in Section 5.1, there are questions about the accuracy of the follow-up times for censored observations in the Duke dataset.

### 6.1.2 Demographics

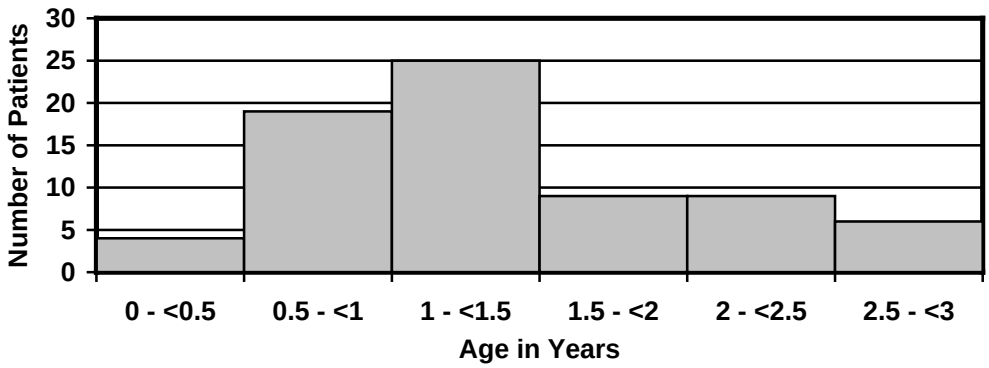
Basic demographic data for the Hurler patients in the pooled datasets are shown below, together with basic treatment data. Demographic information other than age was not provided in the NYBC dataset.

**Table 6: Demographics and Treatment Data for Hurler Syndrome Patients – Docket Data**

| | |
|---|---|
| Total N | 72 |
| Age in Years | |
| Mean (SD) | 1.4 (0.7) |
| Median (range) | 1.3 (0 – 2.9) |
| Gender | |
| Male | 46% (33) |
| Female | 49% (35) |
| Unknown | 6% (4) |
| Race | |
| Caucasian | 81% (58) |
| African/American | 3% (2) |
| Hispanic | 10% (7) |
| Asian Indian | 1% (1) |
| Unknown | 6% (4) |
| Dosing* ($x10^7$ TNC/kg prefreeze) | |
| Median | 10.9 |
| $10^{th}$, $25^{th}$, & $75^{th}$ percentiles | 5.4, 7.1, 14.4 |
| Dose < 2.5 | 0% (0) |
| HLA Match | |
| 6/6 | 14% (10) |
| 5/6 | 43% (31) |
| 4/5 | 35% (25) |
| 3/6 | 6% (4) |
| Unknown | 3% (2) |
| Data source | |
| Duke[1] | 67% (48) |
| NMDP[2] | 28% (20) |
| NYBC[3] | 6% (4) |

[1] Duke count includes 4 cases also reported by NMDP, and 4 cases also reported by NYBC
[2] Excludes 4 cases also reported by Duke
[3] Excludes 4 cases also reported by Duke
* Dose was unknown for 2 patients (3%)

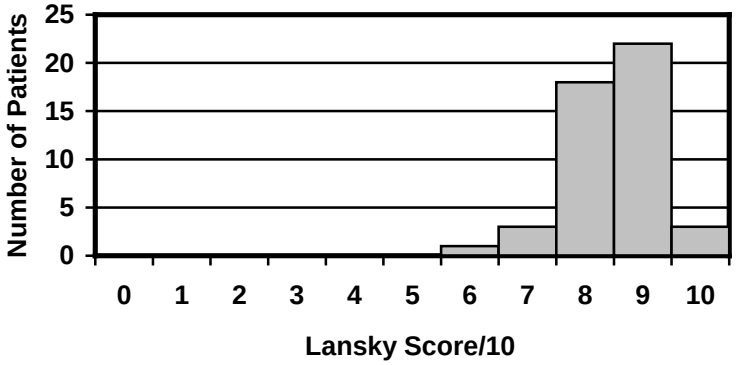
**Figure 1: Age Distribution for Hurler Syndrome Patients – Docket Data**




The age distribution appears to be as expected for patients early in the course of Hurler syndrome. The older patients may represent those for whom UCB transplant was delayed until a year or more after diagnosis, but might also be an indication that some patients with Hurler-Scheie syndrome have been included. Knowing age at diagnosis could have been helpful in determining how well patients fit the classic Hurler syndrome phenotype.

The Lansky score (Lansky and List et al. 1987) is a general play-performance score originally designed for pediatric cancer patients. The score was recorded only in the Duke dataset. The score ranges from 0 to 100 in multiples of 10 (in the Duke dataset, the score was divided by 10). Briefly, on this scale 100 is fully active, 90 is minor restriction in strenuous activity, 80 is active but tires more quickly, 70 is greater restriction and less time spent in play, and 60 is minimal play but busy with quieter activities. The distribution for Hurler patients in the Duke data is shown in Figure 2 below:

**Figure 2: Lansky Score Distribution for Hurler Syndrome Patients – Docket Data**




(Lansky score only for patients reported in Duke dataset. One value coded as 19 was treated as missing.)

### 6.1.3 Subject Disposition

No protocol was provided for this study, and there is no information available about screening, eligibility criteria, or diagnostic criteria. Two patients in the Duke dataset were diagnosed as "Hurler's Scheie" and "Hurler Scheie" with ages given as 0.97 and 2.9 years. They were not included in this analysis. Of the 72 total Hurler syndrome patients, 19 are reported to have died. The causes of death were:

**Table 7: Causes of Death in Hurler Syndrome Patients – Docket Data**

| | N |
|---|---|
| Respiratory | 7 |
| Hemorrhagic | 3 |
| Multisystem | 2 |
| Renal failure | 2 |
| Misc.* | 5 |

* Veno-occlusive disease-1, hyperammonemia-1, acute GVHD-1, Infection, unspecified-1, other, unspecified-1.

For one patient (Duke, (b) (6)), an event of autologous recovery was listed as occurring about three months after transplant, but the follow-up information was unclear: neither a death nor an overall survival time is reported. The demographics above were reported for all available patients, but the survival analysis excludes patient Duke (b) (6) (equivalent to treating her as censored at time 0).

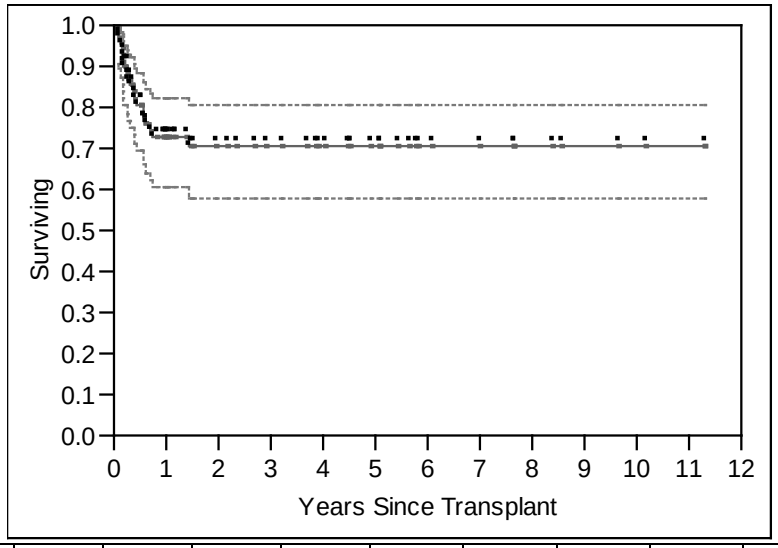
Two patients in the NMDP dataset received a second transplant, one at 39 days due to no engraftment, one at 10 months for an unknown reason. Both were recorded as alive at last report.

### 6.1.4 Analysis of Primary Endpoint(s)

#### Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown below for the 71 analyzable Hurler syndrome patients. There is 27% mortality by the end of the first year. After the first year, additional mortality is very low. The loss to follow-up is greatest in the first year, with progressive censoring through year 6. Median follow-up was 1.1 years; 75$^{th}$ quartile of follow-up was 4.5 years.

**Figure 3: Survival for 71 Hurler Patients Following UCB Transplant – Docket Data**




| Year | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Survival | 1.00 | 0.73 | 0.70 | 0.70 | 0.70 | 0.70 | 0.70 | 0.70 | 0.70 | 0.70 | 0.70 |
| No. at Risk | 71 | 40 | 28 | 24 | 20 | 15 | 9 | 8 | 5 | 3 | 2 |

Staba published a report of 20 Hurler syndrome patients who received UCB transplant at Duke University (Staba and Escolar et al. 2004). It presumably represents a subset of the 48 patients in the Duke dataset. In that experience she reported overall event-free survival of 85% at a median follow-up of 2.5 years. She reported that growth velocity was normal in the majority of patients and that "all children had either stable or improved neurocognitive function after transplantation." There was a developmental lag post-transplant, but "by 72 months [of age] they appeared to be gaining cognitive skills at slightly slower rate (slope = 0.95) than the mean for unaffected children."

The long-term mortality is important in evaluating the efficacy of UCB transplant on survival in order to determine if there is a survival "payoff" for the early mortality risk. To refine the assessment, two modifications were made:

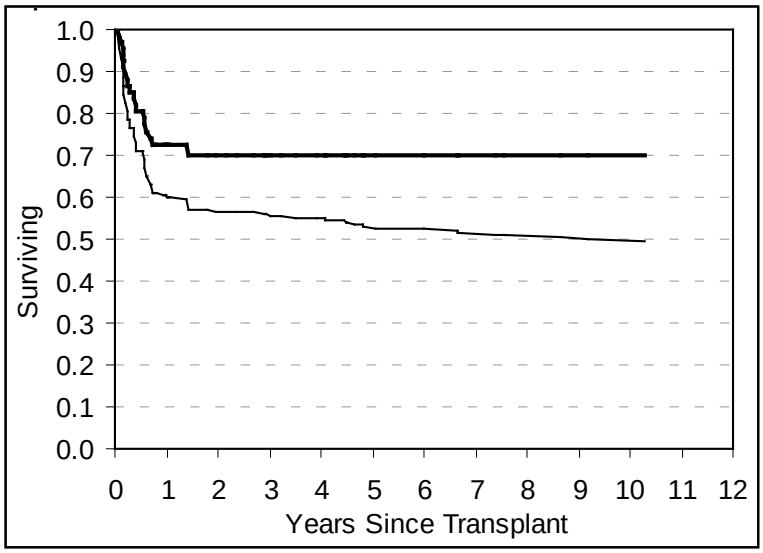
First, the Duke data were adjusted in an attempt to discount for the apparent overstatement for follow-up time for censored patients (that used the date of the dataset rather than time of a last visit as the follow-up time, see Section 3.1). As an approximation, it was assumed that patients might be seen only quarterly for the first year, semiannually in the second and third years, and annually thereafter. A simple conservative approximation to the implied step function is to replace the stated follow-up time, T, by the function T * 2/3 for T < 3 years and T-1 for T ≥ 3 years. Time to death was not adjusted for those who died.

Second, the usual method for estimating the standard error for the Kaplan-Meier curve has the characteristic that no change occurs following the last observed death, even if

this is followed by substantial censoring. That overstates the confidence in the estimates following the last death. A hybrid technique (Borkowf 2005) provides more accurate confidence intervals in this situation.

These modifications result in the survival curve shown below (including only the lower end of the 95% confidence interval). The estimated survival is very similar to that without adjustment, but the confidence limits extend almost 10% lower by the right end of the curve:

**Figure 4: Survival for 71 Hurler Patients Following UCB Transplant with Adjustment to Duke F/U Times – Docket Data**




| Year | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Survival | 1.00 | 0.72 | 0.70 | 0.70 | 0.70 | 0.70 | 0.70 | 0.70 | 0.70 | 0.70 | 0.70 |
| No. at Risk | 71 | 35 | 27 | 21 | 17 | 9 | 8 | 5 | 3 | 2 | 1 |

Survival curves with Duke follow-up time for censored observations discounted (see text). Heavy line is survival estimated by Kaplan-Meier method; light line is lower end of 95% confidence limits using Borkowf hybrid technique.

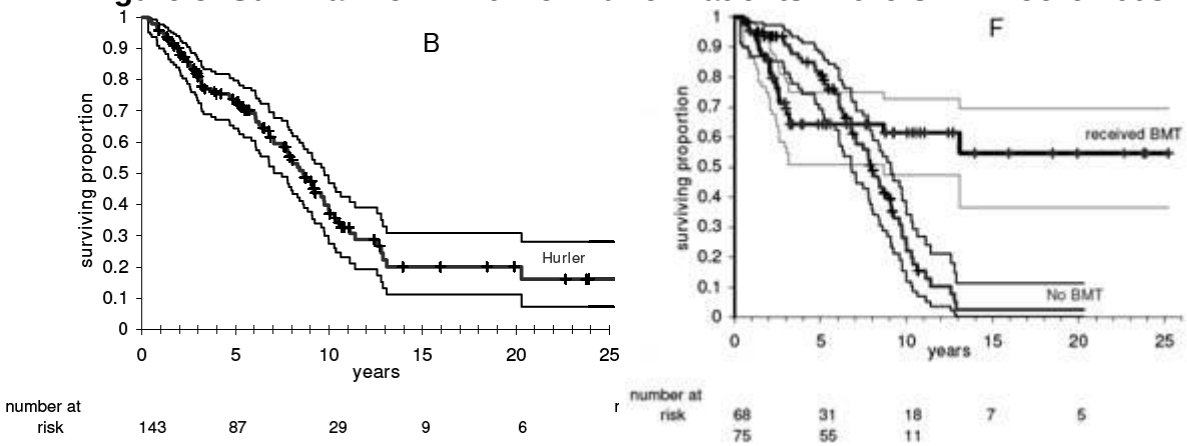
## Historical Experience

Wraith (Wraith and Rogers et al. 1987) reviewed 27 cases of Hurler syndrome seen in Australia between 1950 and 1986. He reported the average age at death was 6.25 years, with a range of 1.3 to 10.9 years. The data are given only as summary statistics without survival curves, and it is not stated whether any received HSCT.

More extensive historical control data come from an analysis by Moore (Moore and Connock et al. 2008). The authors obtained information from a longitudinal dataset maintained for over 20 years by the Society for Mucopolysaccharidosis Disease (UK). Since most MPS I patients are seen at only a few centers in the U.K., the Society

estimates that it has data on most, if not all, MPS I patients in that country. Moore reviewed cases entered between 1981 and 2005 and included only those with births up to 2003, in order to allow for delay in diagnosis. Of the 196 patients in the database, 143 were categorized as Hurler syndrome. Overall survival for these cases is shown as display B in Figure 5 below. Because 65 Hurler syndrome patients received BMT, Moore also computed a survival curve for those 65, as well as a survival curve for all Hurler patients, but treating BMT as a censoring event. These curves are shown as display F in the Figure 5 below:

**Figure 5: Survival from Birth for Hurler Patients in the UK – Moore 2008**




Source: Moore and Connock et al. 2008

A log rank test of the BMT vs. No BMT experience estimated a hazard ratio of 0.58 with p = 0.0004

> *Reviewer's Comment: The assumption of proportional hazards clearly does not apply when survival curves cross, so the hazard ratio number is hard to interpret. Although the test rejects the hypothesis of equal hazards, the question of which one is "better" requires consideration of more than just the hazard ratio estimate*.)

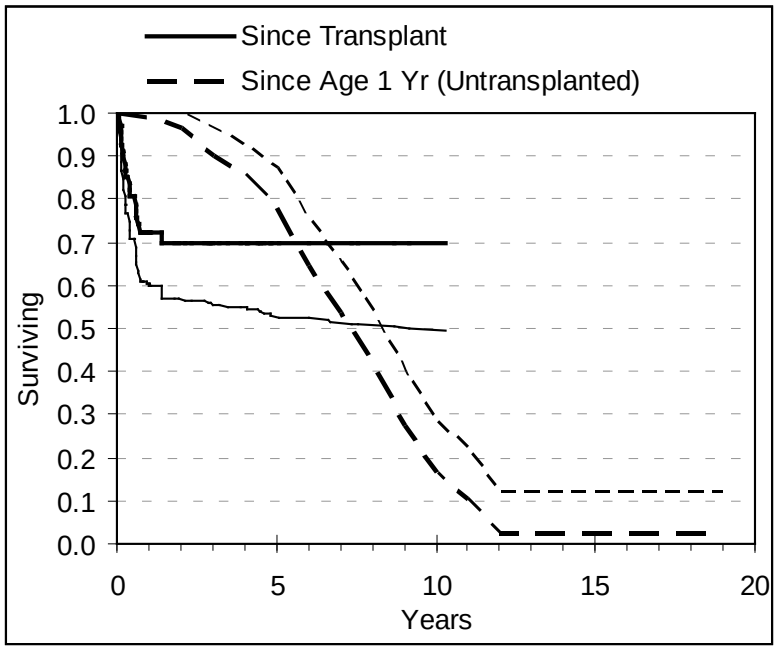
The Moore and Connock paper also showed an overall survival curve for Hurler-Scheie patients. This is not reproduced here, but it is noteworthy that the 10-year survival was about 95%, and 20 year survival was better than 80%. Thus, it is important to be sure that only Hurler syndrome patients are included in the active treatment experience if the Moore control experience for Hurler syndrome is to be used. As mentioned previously, the Duke dataset had evidence that it made the distinction, but only the term "Hurler syndrome" appeared in the NYBC and NMDP datasets. The diagnostic criteria used for making the diagnosis and deciding on the phenotype were not stated for any of the Docket datasets. Without knowing diagnostic or eligibility criteria, it is not known how well these patients fit the diagnosis. Of note, only one of the 16 patients surviving beyond 5 years from transplant came from other than the Duke report (NYBC). For the

historical control patients, it would be valuable to know what the phenotype determination was at the average age at which transplant might have occurred and whether there was any revision of the phenotype designation as the clinical course unfolded.

Since the decision to have BMT is assumed not be randomized in the UK data, the No BMT experience reported by Moore may be subject to selection bias, and the censoring used in calculating the survival curves is unlikely to be uninformative censoring. Given the dates, the exposure to laronidase in the population was probably none to minimal, and Moore reports that only Hurler-Scheie and Scheie patients had received it. The data for the No BMT experience are reasonably consistent with the natural history reported by Wraith and Rogers et al. 1987 as described above. The Moore data appear to be the most complete and detailed historical data available.

Since the control data from the U.K. used by Moore are only published in the form of a graphic, it is not possible to do a log-rank comparison of the docket data vs. the historical controls. In order to compare the active treatment and historical control experiences more directly, the Moore control experience was visually extracted by making measurements on an enlargement of the published graphic. Moore's graph (Figure 5) shows a small probability of death in the first year. Post-transplant experience should be compared to natural history *conditioned on* survival until the age at which transplant occurs. Because patients received UCB at a median age slightly greater than 1 year, the control data were adjusted to represent the natural history of survival for time elapsed since reaching 1 year of age, to approximate the expected survival after the median age of transplant. The superposition of this construction and the post-transplant UCB experience is shown in Figure 6:

**Figure 6: Docket UCB Transplant Experience Compared to Historical Controls for Hurler Syndrome**




| Year | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Survival | 1.00 | 0.72 | 0.70 | 0.70 | 0.70 | 0.70 | 0.70 | 0.70 | 0.70 | 0.70 | 0.70 |
| No. at Risk | 71 | 35 | 27 | 21 | 17 | 9 | 8 | 5 | 3 | 2 | 1 |

Survival following UCB transplant with adjusted follow-up times for Duke dataset (as described in text and shown previously) with overlay of control experience modified to show survival after age 1 year. Lighter solid line is *lower* end of 95% CI (two-sided) for UCB transplant; lighter dashed line is *upper* end of 95% CI for control.

Source: UCB (Transplant) data from Docket, control (Untransplanted) data modified from Moore and Connock et al. 2008

Although lack of individual patient data for the historical controls preclude the usual statistical comparisons, the visually extracted data from the control survival curve can be taken as a set of fixed values for use in a one-sample comparison (Hyde 1977). Using the discounted survival times for the Docket data, the expected number of deaths in patients given UCB is estimated to be 7.4 based on the historical experience, whereas 19 deaths were observed, giving an estimated hazard ratio for UCB vs. control of 2.6. Without discounting survival times the estimated hazard ratio is 2.0. (A nominal one-sample test of significance finds $p < 0.001$, but this is anticonservative because it ignores the uncertainty in the control group.)

*Reviewer's Comments:*
*As was the case for the comparison of BMT to historical controls, the assumption of proportional hazards is not supported because the UCB and control survival curves cross. The reason that apparently similar curves (BMT and UCB) produce opposite relative hazard ratios compared to control (BMT hazard < 1 but UCB hazard > 1) is due to the difference in risk exposure: the relatively longer periods of observation for*

*the BMT patients produce a hazard ratio estimate that is an averaged hazard ratio weighted more toward the later part of the curve where the hazard ratio is lower, whereas the hazard ratio averaging for UCB is more heavily weighted toward the early post-transplant experience due to the shorter follow-up of UCB patients.*

*Based on the data submitted to the Docket, there is early mortality with UCB transplantation in Hurler syndrome, with a break-even point that appears to occur somewhere between 5 and 9 years after transplant, compared to historical controls. However, the follow-up data in the Docket datasets are very sparse at 9 years. In addition, there is an inability to evaluate the comparability of Docket patients and historical controls due to limited individual patient data for both Docket and historical control patients regarding baseline attributes and concurrent therapy. Further, the Docket dataset that provides the majority of the evidence for this disease (Duke dataset) has data quality issues regarding length of follow-up that make the conclusions from those data unreliable.*

*Although the survival curve for UCB appears very similar to that for bone marrow transplant in Hurler syndrome, the similarity is clearest only for the period that includes the high early mortality, but the small numbers of UCB patients followed for at least a decade means there is little evidence by which to judge the similarity to BMT in that extended time frame.*

### 6.1.5 Analysis of Secondary Endpoint(s)

For patients treated at Duke, a dataset was provided that reported enzymes values before and after transplantation with UCB. However, there was no information regarding the specimen, assay, units of measurement, or timing of assessments.

**Table 8: Enzyme Results for Hurler Syndrome Patients – Duke Dataset**

| | Pretransplant (N=41) | Post-transplant (N=35) | Difference (N=32) |
|---|---|---|---|
| Mean (SEM) | 0.5 (0.2) | 63 (5) | 61 (4) |
| Median (Range) | 0 (0 – 5) | 56 (12 – 170) | 58 (25 – 106) |

While it appears that enzyme levels were significantly higher following UCB transplantation, the clinical significance of the finding is unclear.

The potential to substantiate claims for clinical benefits other than survival was not evaluated because no other disease-specific outcome data were included in the Docket datasets.

### 6.1.7 Subpopulations

Of the 72 patients with Hurler syndrome, gender and race data were not recorded for 4 (6%).

In a univariate proportional hazards analysis, survival outcome appeared to be related to age, with an estimated increase in hazard of 68% per year (p = 0.048). The results were essentially the same with adjustment for dose. The effect seemed to be driven by a much higher mortality in the subgroup of 6 patients aged 2.5 years or greater, in which 5 of the patients died within a year of transplant. In a multivariate analysis incorporating age, gender, race, and dose (but omitting the 4 patient with incomplete data), the estimated effect of age was slightly lower (57% per year), and it was not statistically significant (see below).

By proportional hazards analysis, neither gender nor race appeared to be related to survival outcome, either in univariate analyses, or in a multivariate analysis (n = 65) incorporating age, gender, race, and dose, (p = 0.11 for age, p = 0.79 for gender, p = 0.80 for race, and p = 0.94 for dose in the multivariate analysis).

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A univariate proportional hazards model found no significant relationship between dose (as prefreeze TNC/kg) and survival (nominal p = 0.97) with an estimated 0.2% *increase* in hazard for each increase in dose of $10^7$ TNC/kg. The results were similar with an analysis including adjustment for age. There was no patient with a dose < 2.5 x $10^7$ TNC/kg, so a subgroup analysis for that dose range could not be done. An analysis comparing patients with doses above and below the median dose of 10.9 x $10^7$ TNC/kg showed nearly identical survival curves.

### 6.1.10 Additional Efficacy Issues/Analyses

<u>Published Reviews and Opinions</u>

In a review of cord blood banking by an AAP Work Group (Work Group on Cord Blood Banking 1999), the summary of indications for allogeneic stem cell transplantation included Hurler syndrome in the category of “controversial; may be effective in selected patients.” Those conclusions were reflected in the 2005 IOM report on cord blood (Meyer and Hanna et al., 2005). However, the Work Group review did not provide references to specific data in support of that determination. The IOM report cited evidence from Staba and Escolar et al. 2004. More recent reviews of the uses of cord blood are found in Smith and Wagner 2009 and Prasad and Kurtzberg 2010. Prasad reported the status of UCB in severe phenotypes of MPS I as standard of care, and provided a list of references in support: Boelens and Rocha et al. 2009, Martin and Carter et al. 2006, Prasad and Mendizabal et al. 2008, and Staba and Escolar et al. 2004. The Cochrane Collaboration has not reviewed the use of stem cell

transplantation in Hurler syndrome. Search of the literature identified additional primary reports of outcomes experience with UCB in Hurler syndrome: Dusing and Thorpe et al. 2007a, Dusing and Thorpe et al. 2007b, Church and Tylee et al. 2007, and Dusing and Rosenberg et al. 2005. The evidence from these publications is described below.

## Published experience with UCB in Hurler syndrome

*Staba and Escolar et al. 2004 (n=20)*

This is a report of 20 patients with Hurler syndrome transplanted with unrelated cord blood at Duke between 1995 and 2002, and so presumably represents a subset of the patients already considered in the review of the Duke dataset. It offers some additional diagnostic and outcome information that was not in the docket datasets. All patients had undetectable or "extremely low" concentration of α-L-iduronidase, consistent with Hurler syndrome; two were homozygous and seven were compound heterozygous for mutations associated with the severe phenotype of MPS I. The median follow-up was just under 2.5 years, but ranged from 1 to 7.5 years. Survival through the first year was 85% and deaths beyond 1 year were reported. After the first year, growth velocity was "normal in the majority of patients." The authors reported that "all children had either stable or improved neurocognitive function after transplantation," and "by 72 months [of age] they appeared to be gaining cognitive skills at slightly slower rate (slope = 0.95) than the mean for unaffected children." There was no clinically significant cardiac dysfunction, but several patients required orthopedic procedures. Although development was compared to normal controls in the form of normative charts, the report did not provide a comparison to objective untransplanted Hurler syndrome control data.

*Dusing and Rosenberg et al. 2005 (n=2)*

This reported on two patients who received UCB for Hurler syndrome at Duke and had motor assessments through 10 months post-transplant. They observed that both children gained new skills but gross motor skills were less advanced than fine motor skills. There were no pretransplant evaluations for comparison. The report did not provide objective untransplanted Hurler syndrome control data for comparison.

*Martin and Carter et al. 2006 (n=21)*

This a report of 69 patients with lysosomal and peroxisomal storage disorders who received UCB transplantation under the COBLT study sponsored by NHLBI. Almost all (67) were transplanted at Duke. The population included 21 patients with Hurler syndrome, who are presumably a subset of the patients already considered in the review of the Duke dataset. The report presents summaries of engraftment, survival, toxicity, and GVHD, but results are not broken down by disease. For the entire group, survival was 80% at 6 months and 72% at one year. Survival was not statistically significantly associated with age, cell dose CD34+ dose, performance status, or HLA match number, but it was significantly worse in non-Caucasians and in those who

received units as part of an expanded access program. The article does not provide efficacy information specifically for Hurler syndrome patients.

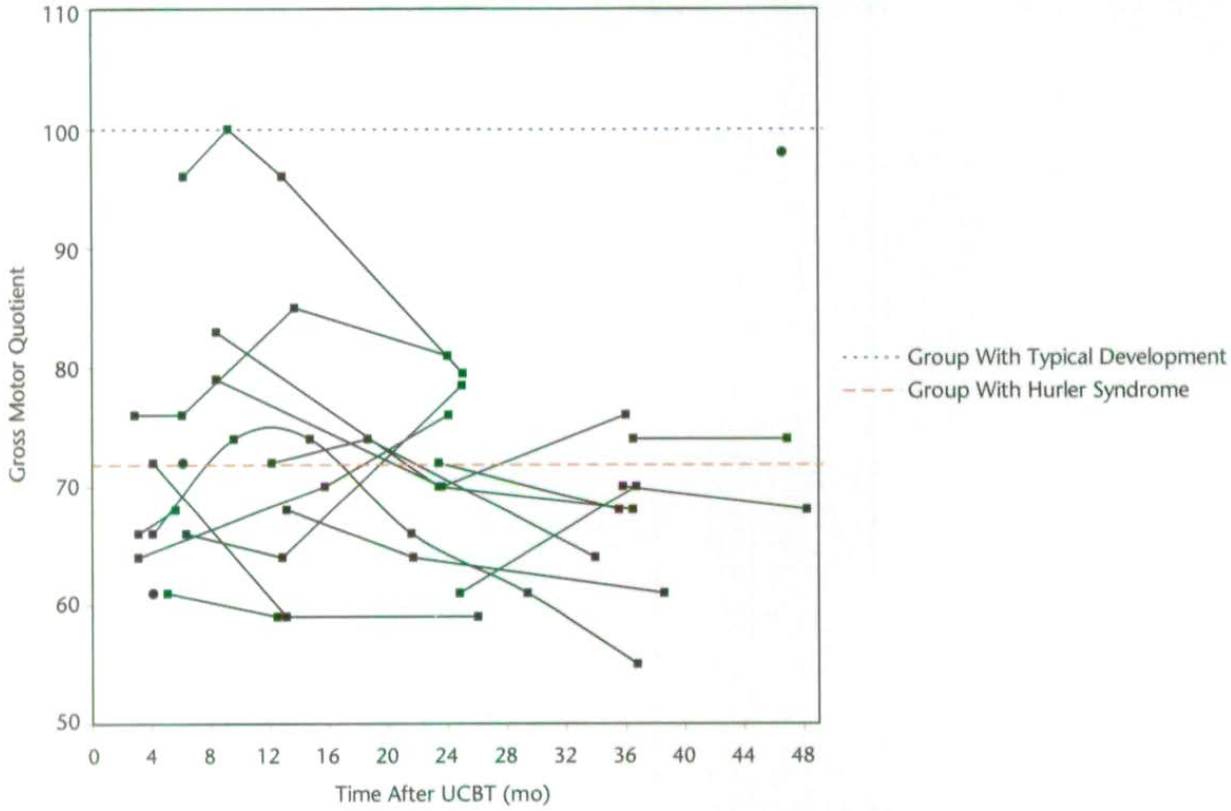
*Dusing and Thorpe et al. 2007a (n=18)*

This reported on 18 Hurler syndrome patients who received UCB transplant and had longitudinal gait assessments. The patients were seen at Univ. of North Carolina and apparently were transplanted at Duke. A group of 438 normal children were used as controls. The Hurler syndrome patients were selected on the ability to walk 50 ft without assistive devices; 13 of them were receiving physical therapy at the time of at least one assessment, most of them weekly. The authors found the Hurler syndrome patients had slower gait speed and shorter step length than normals at ages 2 and 3 years, but were similar to normal controls at 4 years. In post hoc analyses, time since transplant, but not age, was associated with normalization of these two parameters. The authors acknowledged that lack of an untreated Hurler syndrome control group limited the ability to assess the effect of UCB on the parameters, and lack of a non-Hurler syndrome UCB group limited the ability to assess how much of the early deficits were attributable to the disease vs. the transplantation experience.

*Dusing and Thorpe et al. 2007b (n=21)*

This reported on 21 Hurler syndrome patients who received UCB at Duke at a mean age of 17 months. It included 15 patients from the previous report (Dusing and Thorpe et al. 2007a); 2 had received UCB before symptoms developed. Patients were assessed for up to 4 years following UCB, with an average of 2.6 assessments per patient. Motor performance score was expressed as a percentage of normal scores based on 2,003 typically developing children. Using the Peabody Developmental Motor Scales, the authors found the Hurler syndrome patients' average gross motor quotient was 72% of normal and did not show any trend toward improvement, relative to development in normal children, between 0 and 4 years after transplant (see Figure 7). Of the subscores, locomotion showed a trend toward relative improvement, stationary skills showed a trend to relative worsening, and object manipulation skills showed no relative trend, compared to the development in normal children (none of these trends was statistically significant). The authors acknowledged that information on the natural history of gross motor abilities in Hurler syndrome is limited, and the findings were not compared to children with Hurler syndrome who had not received UCB. Lack of a non-Hurler syndrome UCB group limited the ability to assess how much of the early deficits was attributable to the disease vs. the transplantation experience.

**Figure 7: Gross Motor Development in Children with Hurler Syndrome Following UCB Transplantation – Dusing 2007**




Changes in gross motor quotient (GMQ) after umbilical cord blood transplantation (UCBT). Solid lines represent 18 children with Hurler syndrome who were assessed multiple times using the Peabody Developmental Motor Scales, second edition (PDMS-2). Each square marker represents the GMQ at the assessment time after UCBT. The solid circles represent an additional 3 children who had only a single assessment. The large dashed red line represents the average GMQ for the children with Hurler syndrome, as derived from the hierarchical linear models. The small dashed blue line represents the mean GMQ on the PDMS-2 for children who were developing typically.
Source: Dusing and Thorpe et al. 2007b

*Church and Tylee et al. 2007 (n=6)*

This article examined 39 patients with Hurler syndrome from Manchester and Dublin at least one year following UCB or bone marrow transplant to assess α-L iduronidase activity and urinary glycosaminoglycans. Of the 6 patients who had UCB, all had full donor chimerism (>95% donor cells). The group of 19 patients with full chimerism had the highest enzyme levels, and enzyme level was inversely related to the urinary dermatan sulphate/chondroitin sulphate ratio. The authors noted "It is notoriously difficult to determine clinical outcome in these patients after transplant. However, we believe that before our data can be used to influence current transplant practice, including donor selection criteria, clinical outcome scores should be correlated with different variables, including biochemical outcome such as we detail."

*Prasad and Mendizabal et al. 2008 (n=45)*
This is a report of 159 patients who received UCB transplantation at Duke, including 45 patients with Hurler syndrome. This appears to consist of patients whose data were also submitted to the Docket and therefore does not appear to provide additional evidence regarding survival. Most results are presented for the study population as a whole. However, the Hurler-specific data showed a 75% survival between 2 and 10 years, with a median follow-up of 5.8 years; the survival experience for Hurler syndrome was similar to that already reported above in Figure 3.

The report did offer some outcome information in additional to survival. There was 89% engraftment with high (>90%) donor chimerism. Other results for the Hurler syndrome patients are reported in the paragraph cited below:

> In this series, 45 patients with severe phenotype Hurler syndrome (MPS I) underwent transplantation and have now been followed for a median of 5.6 years (range, 1-11 years). All of the surviving patients have experienced disease stabilization and most continue to gain cognitive skills. All children of sufficient age attend school, with 81% placed in age-appropriate classes. Most of the patients with average IQ have required an aide in the classroom to help them attend to tasks. All but 2 children experienced stabilization or improvement of corneal clouding. Orthopedic problems have progressed in many children, with some requiring surgical correction. A total of 3 children had surgery for carpal tunnel syndrome, 4 for back or spine, 2 for hip problems, and 2 for knee problems. A total of 2 children have been treated with growth hormone for short stature and 2 (1 boy, 1 girl) have developed precocious puberty. A total of 2 children have also developed Hurler-associated retinal disease. (Prasad and Mendizabal et al. 2008)

The article does not state how the diagnosis of Hurler syndrome was established or criteria used to determine eligibility for transplant, and no comparisons to specific untreated Hurler control data were provided.

> *Reviewer's comment: Because the transplantation center is Duke, this report is presumed to include the same patients reported in the Duke database, and therefore provides no additional evidence regarding survival beyond what was reviewed in Section 6.1.4. The Duke dataset included 48 patients with Hurler syndrome, was dated 4/17/07, and was received in the Docket on 5/18/07; the article was submitted to the journal on 3/15/08, almost a year later. It is unclear why only 45 patients are reported in the article.*

*Boelens and Rocha et al. 2009 (n=93)*
This article is a retrospective report on 93 patients with Hurler syndrome who received UCB transplantation. It is a composite of the Duke and Eurocord experience and included 47 patients from Duke, with the remaining patients coming from 18 international centers and one other U.S. site (Minneapolis). The article states that 40 patients were previously published. Median patient age was 1.3 years. At 3 years, overall survival was 77% and event-free survival (EFS, defined by time to autologous

reconstitution, graft failure, retransplant, or death) was 70%. Six had autologous reconstitution and 5 had graft failure. Survival rates beyond 3 years are not reported. Of 58 patients with chimerism data at last follow-up, 97% had full donor chimerism. EFS was positively related to shorter interval from diagnosis to transplant, conditioning regimen using busulfan and cyclophosphamide. There was a trend toward better EFS with HLA match, but HLA match did not predict acute or chronic GVHD. Neither cell dose nor prior enzyme replacement therapy predicted survival. Acute GVHD was associated with a higher ($> 7.6 \times 10^7$) cell dose.

*Reviewer's Comment:*
*Evidence from published data regarding the effect of UCB on other aspects of Hurler syndrome is limited by the lack of objective comparisons to controls and by susceptibility to possible selection or reporting bias. Additional experience from publications does confirm early mortality rate but has limited duration of follow-up (~3 years).*

## 6.2 Krabbe Disease

Krabbe disease (globoid cell leukodystrophy) is an autosomal degenerative neurologic disease caused by deficiency of the enzyme galactocerebrosidase (GALC). It is due to a mutation of the GALC gene on chromosome 14q31. Diagnosis is made by enzyme assay in leukocytes or cultured fibroblasts. The incidence is estimated at 1 in 100,000 live births (Duffner and Jalal et al. 2009).

The phenotype is highly variable and clinical course seems to correlate strongly with age of onset, whereas level of enzyme activity and (generally) mutation do not correlate with phenotype (Duffner and Jalal et al. 2009). Over 60 mutations have been identified, but only a few have been associated with the most severe form of the disease; one mutation (C502T, a large deletion) appears associated with the early infantile onset form and may account for a third of such cases (Kemper and Knapp et al. 2010).

The early infantile onset form presents in the first six months of life with developmental delay, hypotonia, absent reflexes, optic atrophy, and microcephaly. Patients deteriorate rapidly, developing seizures and tonic extensor spasm, and typically die by two years of age (Wenger and Suzuki et al. 2001). Late infantile and juvenile forms present later in life and are more variable in progression, but patients usually die two to seven years after diagnosis. Based on about 400 cases referred to his lab for diagnosis, Wenger estimated that 85% to 90% of cases are infantile onset type (Wenger and Rafi et al. 2000). However, of the cases in the Krabbe Family Database, only 71% had onset in the age range 0 to 6 months (Duffner and Jalal et al. 2009).

Loes and Peters et al. 1999 evaluated MRI findings in 22 patients with Krabbe disease, 5 of whom had more than one serial assessment. Three patients, age range 16 months to 8 years) were asymptomatic. Patients were classified as early onset or late onset based on whether symptoms presented at 2 years of age or younger. They found that cerebellar white matter and deep gray matter abnormalities were seen only in early onset disease and the posterior corpus callosum and parieto-occipital white matter abnormalities were more common in older onset patients. Pyramidal tract involvement was seen in both groups.

> *Reviewer's comment: The paper did not distinguish between early infantile and late infantile forms, and the presence of 6 patients with onset listed as 6 months makes that division difficult. The paper did not evaluate the ability of presymptomatic MRI to predict clinical course. The paper did not provide any calculation of sensitivity or specificity, and any such estimates based only on the patients in the report would have been subject to training set bias.*

Husain and Altuwaijri et al. 2004 correlated neurophysiologic studies with MRI findings in 26 patients of whom 20 were early infantile onset. They observed that nerve conduction abnormalities may be seen before other neurophysiologic findings in early

onset disease, but nerve conduction abnormalities were less common and less predictable in late onset disease. They did not propose that such studies could predict phenotype in asymptomatic patients. The report by Zafeiriou and Anastasiou et al. 1997 underscores the difficulty in correlating MRI with phenotype.

Escolar and Poe et al. 2006 developed a 4-point staging system based on a categorization of specific clinical findings in order to predict post-transplant outcomes (predominantly cord blood). They found that patients with Stage 3 or 4 (moderate to severe neurologic involvement or advanced disease) had higher mortality or more severe disability following transplant, and they recommended that only patients in Stages 1 or 2 be considered for transplant.

There is no approved drug or biologic therapy for Krabbe disease. No specific therapy appears to be effective for infantile forms once a patient has become symptomatic, but a published report (Escolar and Poe et al. 2005) has suggested that UCB before onset of symptoms can be beneficial. In 2006, New York state began a screening program for Krabbe disease (Duffner and Caggana et al. 2009; Kemper and Knapp et al. 2010).

### 6.2.1 Methods

Efficacy was evaluated by computing estimates for post-transplant survival obtained from pooling the three datasets described in Section 5.1. Results were compared to historical control survival data obtained from the literature. The literature was reviewed for additional reports of experience with unrelated cord blood use for Krabbe disease.

Diagnostic information, other than the stated diagnosis of Krabbe disease, was not provided in the Docket datasets. Thus, eligibility criteria for the series and the criteria used for classification of the phenotype, particularly the early infantile onset phenotype, are unknown. Although the Lansky scores (see below) recorded in the Duke dataset give some indication of patient status, there is no explicit representation of whether or not a patient had neurologic symptoms at the time of UCB transplantation. Other than post-transplant enzyme concentrations, information on disease-specific outcomes that might have been of interest, such as neurologic changes, was not provided. Almost all (95%) of the cases came from the Duke dataset, for which there are questions about the accuracy of the follow-up times for censored observations (see Section 5.1).

### 6.2.2 Demographics

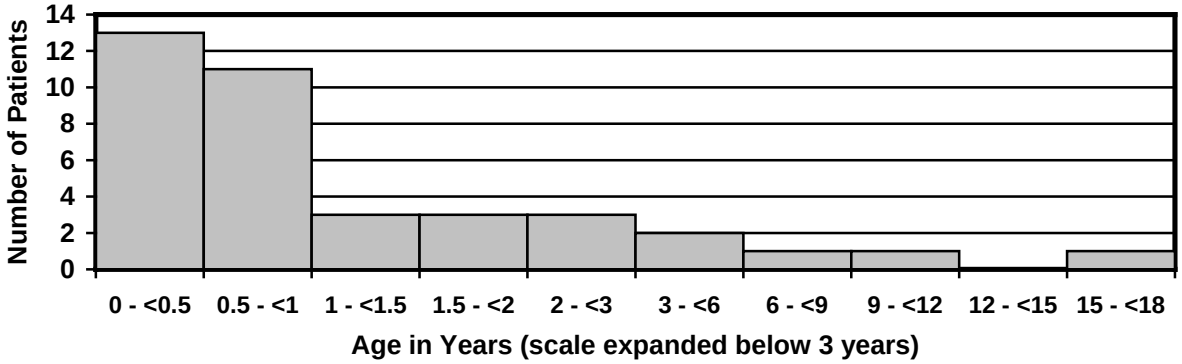
Basic demographic data for the Krabbe disease patients in the pooled datasets are shown in the table below, together with basic treatment data. Demographic information other than age was not provided in the NYBC dataset.

**Table 9: Demographics and Treatment Data for Krabbe Patients – Docket Data**

| | |
|---|---|
| Total N | 38 |
| Age in Years | |
| Mean (SD) | 1.8 (3.2) |
| Median (Range) | 0.7 (0.05 – 16.7) |
| Gender | |
| Male | 58% (22) |
| Female | 39% (15) |
| Unknown | 3% (1) |
| Race | |
| Caucasian | 79% (30) |
| African or African/American | 11% (4) |
| Hispanic or French/Hispanic | 5% (2) |
| Unknown | 5% (2) |
| Dosing (x$10^7$ TNC/kg prefreeze) | |
| Median | 16.5 |
| $10^{th}$, $25^{th}$, & $75^{th}$ percentiles | 6.0, 9.2, 21.8 |
| Dose < 2.5 | 3% (1) |
| HLA Match | |
| 6/6 | 3% (1) |
| 5/6 | 37% (14) |
| 4/5 | 58% (22) |
| 3/6 | 3% (1) |
| Data source | |
| Duke[1] | 95% (36) |
| NMDP[2] | 3% (1) |
| NYBC[2] | 3% (1) |

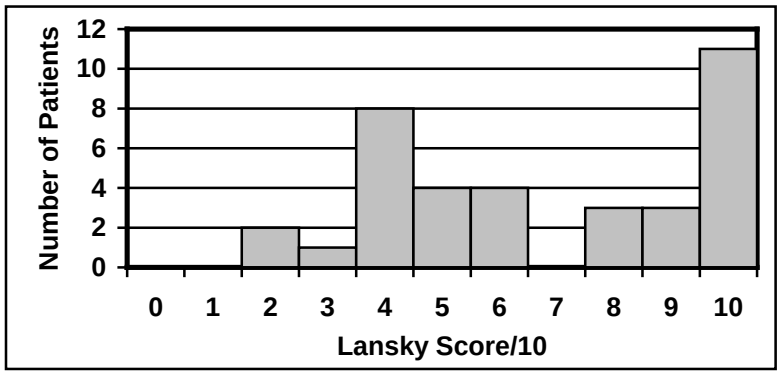
[1] Duke count includes one case each also reported by NMDP and NYBC
[2] Excludes cases also reported by Duke

**Figure 8: Age Distribution for Krabbe Disease Patients – Docket Data**




The Lansky score is a play-performance score (see discussion under 6.1.2). It was only recorded in the Duke dataset. The distribution of scores for those 36 patients is shown in Figure 9 below.

**Figure 9: Lansky Score Distribution for Krabbe Disease Patients – Docket Data**




(Lansky score only for the 36 patients in Duke dataset.)

It is noteworthy that there are 8 patients (21% of the total) who are older than two, of whom 3 were older than 6 years. This would be unusual for infantile onset Krabbe disease other than for a patient in the most advanced stage, who would seem to be an unlikely prospect for transplantation. Further, just under half of the Duke dataset patients had a score of 80 (active but tires more quickly) or better. The rest fell in the range of 20 (often sleeping) to 60 (minimal active play) with a mode of 40 (mostly in bed). All 6 of the patients aged 2 years or older in the Duke dataset had a Lansky score of 60 or better. Thus, it appears likely there was a substantial representation of phenotypes other than infantile onset type.

### 6.2.3 Subject Disposition

No protocol was provided for this study, and there is no information available about screening, eligibility criteria, or diagnostic criteria. Of the 38 total Krabbe disease patients, 17 are reported to have died. Causes of death are listed in Table 10 below:

**Table 10: Cause of Death for Krabbe Disease Patients – Docket Data**

| | N |
|---|---|
| Respiratory | 8 |
| Sepsis | 2 |
| Progression of Krabbe Disease | 2 |
| Misc.* | 5 |

* Hemorrhage-1, GVHD-1, multi-organ failure-1, “PD” [progression of disease?]-1, “RECUR/RESDL LEUK”-1

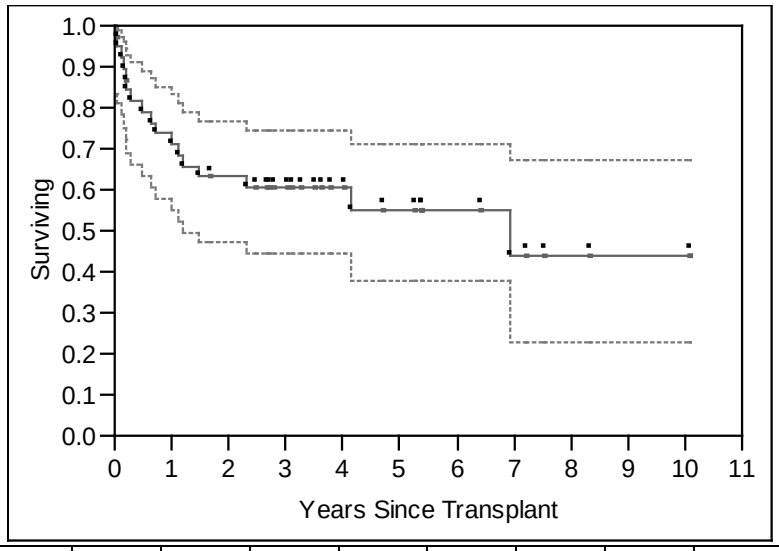
Two of the causes of death classified as respiratory were noted to be secondary to progression of Krabbe disease. One patient (whose death was attributed to “recur/residual leukemia”) received a second transplant due to lack of engraftment.

### 6.2.4 Analysis of Primary Endpoint(s)

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown in Figure 10 below for the 38 Krabbe disease patients from the pooled Docket datasets. Mortality is 29% in the first year. The mortality rate is lower, but still progressive, in subsequent years. Censoring is heaviest between 2 and 4 years. The median follow-up was 2.8 years.

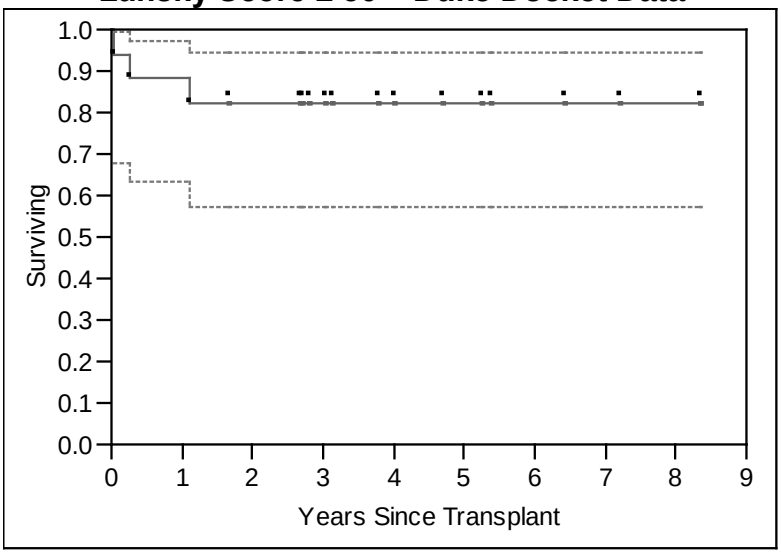
**Figure 10: Survival Following UCB Transplant in 38 Krabbe Disease Patients – Docket Data**




| Year | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Survival | 1.00 | 0.71 | 0.63 | 0.60 | 0.60 | 0.55 | 0.55 | 0.44 | 0.44 | 0.44 | 0.44 |
| No. at Risk | 38 | 27 | 23 | 18 | 12 | 9 | 6 | 4 | 2 | 1 | 1 |

Current treatment recommendations in the literature (Prasad and Kurtzberg 2010) stress the importance of performing HSCT before onset of symptoms. Although symptoms are not recorded in the databases, the subset with Lansky score ≥ 80 (only available for the Duke dataset) was analyzed separately, as an approximation to selecting an asymptomatic or minimally symptomatic population. Note that this subset includes 6 patients who were at least 2 years old. The survival experience for the group is shown in Figure 11 below:

**Figure 11: Survival Following UCB Transplant in 17 Krabbe Disease Patients with Lansky Score ≥ 80 – Duke Docket Data**




A subset of 25 of the Duke patients was analyzed in the publication by Escolar (Escolar and Poe et al. 2005). Because the publication also included an historical control group, it is discussed in the following section.

There were 8 patients in the dataset who were age 2 years or older and who presumably represented milder phenotypes. A separate plot for these 8 is not shown, but half of them died, all within the first year following transplant. Follow-up for the 4 survivors ranged from 3.0 to 5.4 years.

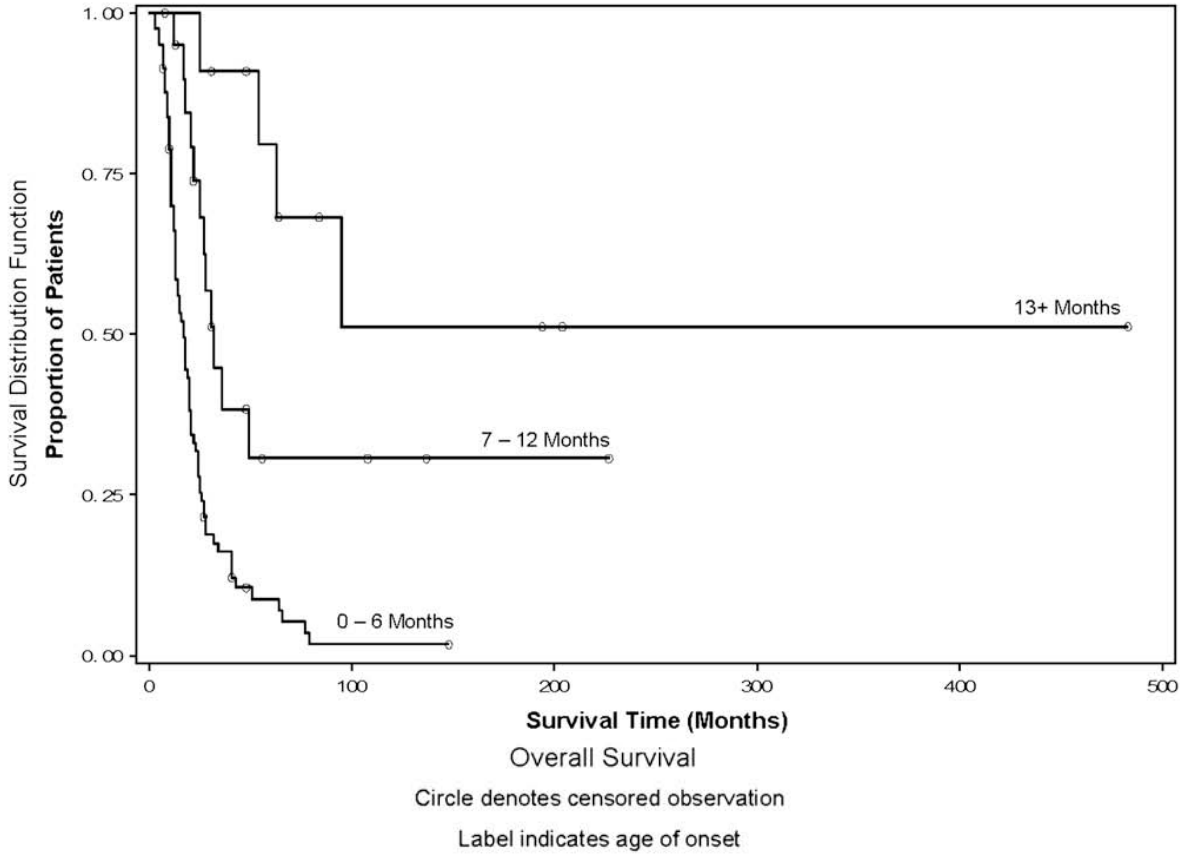
## Historical Experience

One of the earliest historical series is presented in a publication that reviewed 32 Swedish cases from 1953 through 1967 (Hagberg and Kollberg et al. 1969). Individual patients' timelines were presented graphically, but were not subjected to statistical analysis. Of the 32 cases, all but one had onset of symptoms by 6 months. The median time of death was about 1 year; two survived beyond age 2, but all were dead before age 3 years.

The largest collection of historical data on Krabbe disease is that obtained by the Hunter's Hope Krabbe Family Database, which began in 1997 (Duffner and Jalal et al. 2009). The data were collected from questionnaires sent to families. As of June 2006, a total of 334 questionnaires had been received. There were 114 cases with information about age of symptom onset. (The authors noted that age at diagnosis was greater and percent of deaths was lower in the excluded cases, but that overall survival functions were not significantly different.) These 114 cases included 81 cases with symptom onset on or before 6 months, 22 cases with symptom onset from 7 through 12

months, and 11 cases with onset at 13 months or later. An analysis of survival by age of symptom onset showed evident differences between these groups (Figure 12, below). The survival analysis did not include patients who had received HSCT. The authors noted the survival experience appeared to be somewhat better than that reported by Hagberg, which they felt could be attributable to improvements in routine care.

**Figure 12: Survival by Age of Symptom Onset in Krabbe Disease from Hunter's Hope Krabbe Family Database**

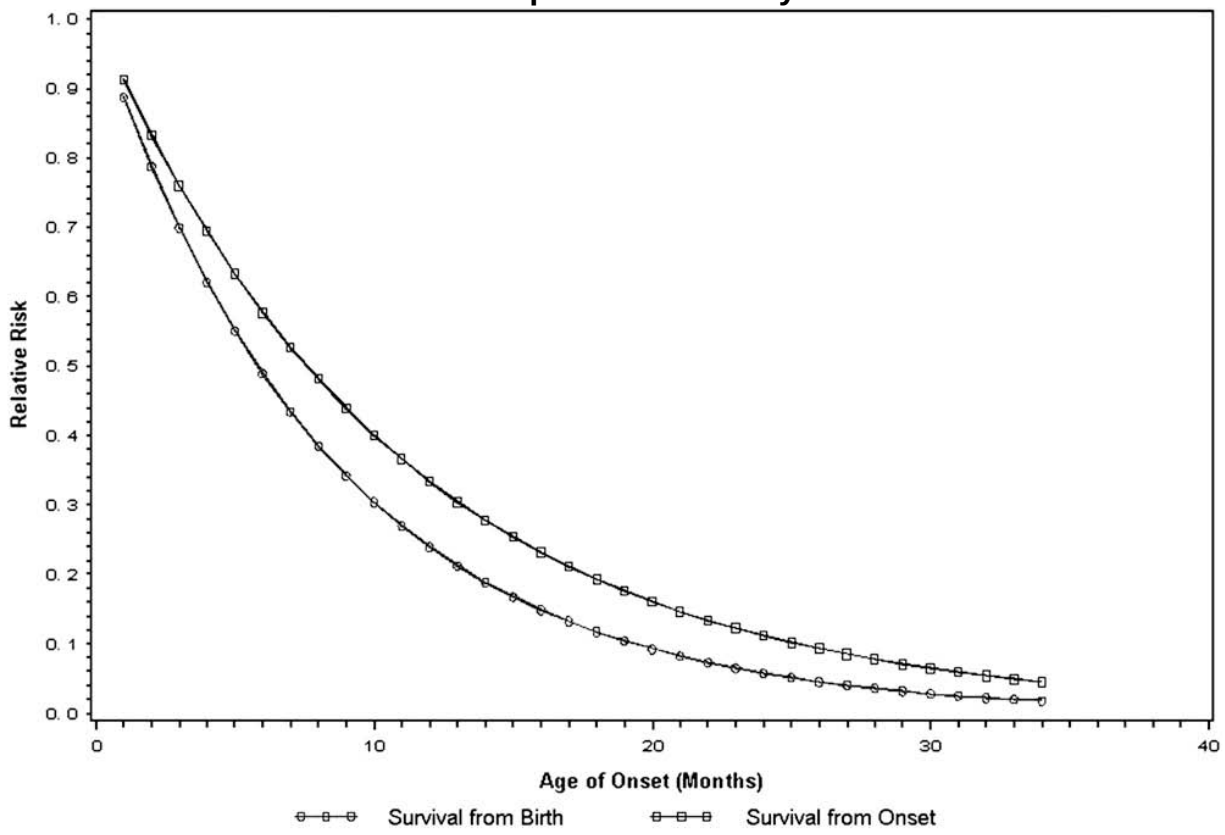



Overall survival (Kaplan–Meier curve). Survivals (in months) differed significantly according to age at onset of symptoms. Age at onset 0-6 mo (n = 81): mean survival = 24.10 mo (standard error of the mean [SEM] = 2.82), median = 17. Age at onset 7-12 mo (n = 22): mean survival = 88.81 mo (SEM = 24.10), median = 32. Age at onset 13+ mo (n = 11): mean survival = 278.75 mo (SEM = 89.02, median > 483 (note that median could not be estimated because less than half of the cases were expected to have died, but the median is known to be greater than the given value, which is the longest survival time of those who did die in this category). Pairwise comparisons (log-rank tests) were also significant: Age of onset 0-6 vs. 7-12 mo., P = 0.0003; 0-6 vs. 13+ mo., P = 0.0001; and 7-12 vs. 13+ mo., P = 0.0400.

Source: Duffner and Jalal et al. 2009

A modeled analysis of relative risk of death as a function of age of onset likewise found a strong association, as shown in Figure 13 (relative risk was calculated relative to the risk for patients whose symptoms began in the first month).

**Figure 13: Relative Risk of Death by Age of Onset for Krabbe's Disease from Hunter's Hope Krabbe Family Database**




Source: Duffner and Jalal et al. 2009

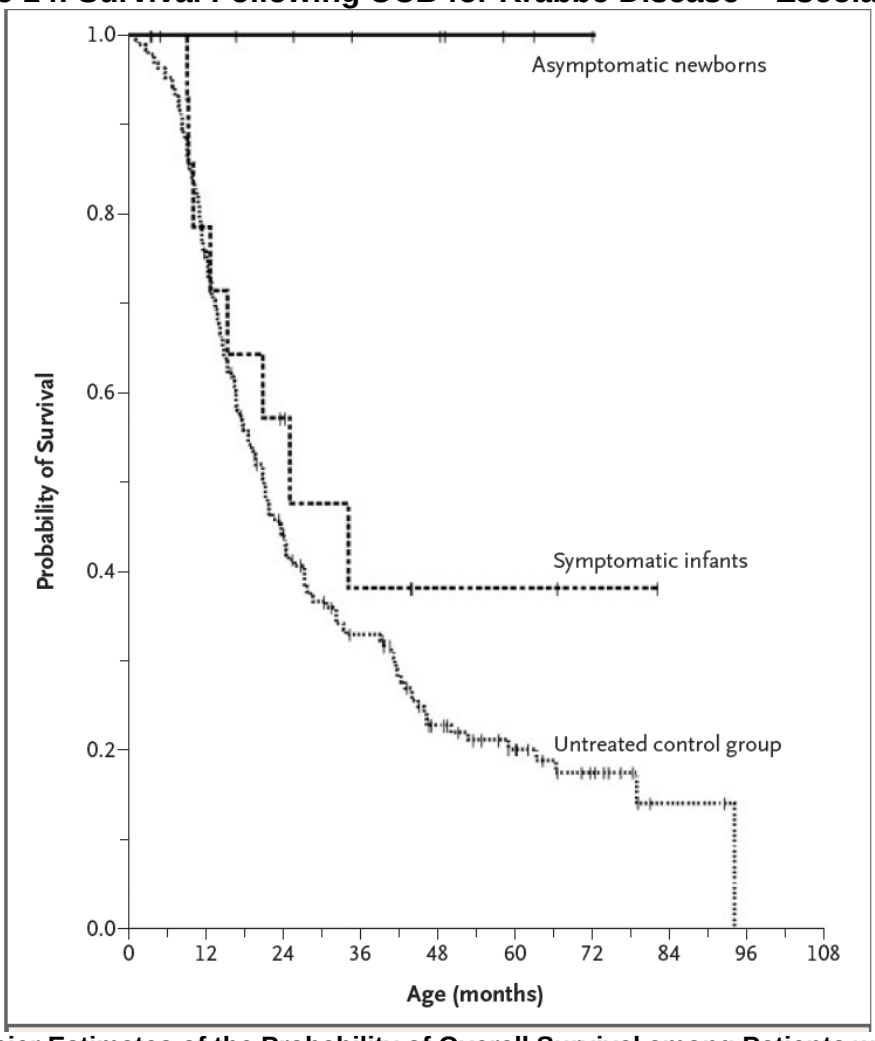
These analyses underscore the high variability in phenotype and the importance of age of symptom onset in estimating prognosis. Although the group of patients with onset at age 6 months or earlier has high mortality, a visual estimate from Figure 12 shows that about 16% survive for 4 years (48 months).

The overall experience for the 38 patients in the Docket dataset yielded an estimate of 60% survival at 4 years and about 44% survival at 100 months (~ 8 years), which would put it between the two later onset curves in Figure 12. In the absence of knowing the age of symptom onset for the Docket data, but considering the ages reported for age at transplant, the UCB transplant experience in the Docket datasets probably reflects a mixture of phenotypes and does not appear strikingly different from the historical data.

As mentioned above, a subset of the Krabbe disease patients in the Duke dataset was analyzed in a published report (Escolar and Poe et al. 2005) that forms the primary basis for the current therapeutic recommendations in the literature. In that analysis, 11 asymptomatic newborns ages 12 to 44 days, and 14 symptomatic infants ages 142 to 352 days, received UCB transplantation. Follow-up ranged from 4 months to 6 years. All 11 asymptomatic newborns survived through a median follow-up of 36 months. The publication also presented a control survival curve obtained for an analysis of 190

patients from the Hunter's Hope Krabbe Family database that were collected through 1/28/05. Further details on selection of the control group were not provided. The survival curves from the publication are shown in Figure 14 below.

**Figure 14: Survival Following UCB for Krabbe Disease – Escolar 2005**




**Kaplan–Meier Estimates of the Probability of Overall Survival among Patients with Krabbe's Disease.**

Shown are Kaplan–Meier estimates of survival among all 11 asymptomatic newborns with Krabbe's disease who underwent transplantation of umbilical-cord blood from unrelated donors, as compared with 6 of 14 infants who underwent transplantation after the development of clinical symptoms (P=0.01) and 190 untreated affected babies (P=0.001). P=0.28 for the comparison between the symptomatic infants and the control group. The tick marks indicate the most recent follow-up for each patient.

Source: Escolar and Poe et al. 2005

*Reviewer's Comments:*

*The Duke dataset in the Docket includes only 9 patients with ages listed as 44 days (0.121 years) or less. The next two older patients were 55 and 117 days. Two of*

*the nine were transplanted after the date of the article, and one of these died a month after transplant. The NMDP dataset also show a death in a neonate two weeks after transplant. Thus, the favorable experience reported by Escolar cannot be confirmed exactly with the Docket datasets, and, with the additional early deaths added to the experience, the estimated treatment effect is diminished. Additional follow-up information on these patients is provided in the publication by Duffner and Caviness, Jr. et al. 2009, which is described below in the review of published experience.*

*The symptomatic patients were transplanted between the ages of about 5 and 12 months. Any analysis of post-transplant survival is an analysis of survival conditional on the fact that the patient has survived at least until the age of transplant. Therefore, the survival of a patient following transplant should be compared with the natural history only for patients who have survived to the age at which the transplant occurred, rather than being compared to all patients. The detailed control data are not available to permit the conditional survival probability to be computed for each transplant, but if one rescales the control survival curve upward, so that it has a probability of 1.0 at about 8 months, it approximately represents survival conditional on being alive at the average age of transplant in the symptomatic group. With that adjustment, the control curve overlaps the symptomatic infant curve very closely through about 3 years, in which case there is not even a trend toward a survival benefit in that group.*

*The comparison of the asymptomatic newborn experience with the control has the advantage of a clear and objective endpoint, but suffers from other deficiencies of an external control comparison, most significantly, the difficulty in establishing the comparability of study populations. The Hunter's Hope database could be subject to ascertainment bias, and the data come from family reports, rather than medical records. The Hunter's Hope analysis presented previously also showed a wide variability in survival with phenotype. In the small group of patients who were transplanted at Duke before symptom onset, the clinical phenotype is undetermined. Absent a randomized comparison to provide statistical comparability, or a series that is consecutive, minimally- or non-selective, and sufficiently large such that the usual epidemiologic distribution of phenotype frequency might be relied upon to provide a reasonable assurance of comparability of the populations, an outcome such as that observed in the Escolar publication (which is less dramatic with additional experience included – see Reviewer's comments above) is still subject to the concerns raised by the use of an external control population. The lack of even a suggestion of survival benefit for the symptomatic patients provides some grounds for additional concern about effectiveness. In addition, 90% of the data for this disease come from the Duke dataset, which has integrity issues regarding length of follow-up.*

### 6.2.5 Analysis of Secondary Endpoint(s)

For patients treated at Duke, an affiliated dataset was provided that reported enzyme values before and after transplantation with UCB. However, there was no information regarding the specimen, assay, units of measurement, or timing of assessments.

**Table 11: Enzyme Results for Krabbe Disease Patients – Duke Dataset**

| | Pretransplant (N=35) | Post-transplant (N=31) | Difference (N=30) |
|---|---|---|---|
| Mean (SEM) | 0.2 (0.2) | 3.3 (0.3) | 3.0 (0.4) |
| Median (Range) | 0.1 (0.0 – 5.5*) | 3.1 (0.9 – 6.9) | 3.0 (-3.1* – 6.9) |

* One patient had a pretransplant value of 5.5, which differed markedly from the others; that patient's post-transplant value was 2.4.

While it appears that enzyme levels were significantly higher following UCB transplantation, the clinical significance of the finding is unclear.

The potential to substantiate claims for clinical benefits other than survival was not evaluated because no other disease-specific outcome data were included in the Docket datasets.

### 6.2.7 Subpopulations

Of the 38 patients with Krabbe disease, gender was not recorded for 1 (3%), and race was not recorded for 2 (5%).

In a univariate proportional hazards analysis, survival outcome appeared to be related to race grouping, with Hispanic+French/Hispanic having the highest hazard, African+African/American in the middle, and Caucasian having the lowest hazard ($p < 0.01$). However, the differences became statistically insignificant ($p = 0.13$) with dose added as a factor, or in a multivariate analysis adding age, gender, and dose (see below).

By proportional hazards analysis, neither age nor gender appeared to be related to survival outcome, either in univariate analyses, or in a multivariate analysis ($n = 36$) incorporating age, gender, race, and dose ($p = 0.72$ for age, $p = 0.94$ for gender, $p = 0.16$ for race, and $p = 0.25$ for dose in the multivariate analysis).

### 6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A univariate proportional hazards model found no significant relationship between dose (as prefreeze TNC/kg) and survival (nominal $p = 0.21$), with an estimated 3.5% decrease in hazard for each increase in dose of $10^7$ TNC/kg. The results were similar with an analysis adjusting for age. There was only one patient with a dose < 2.5 x $10^7$ TNC/kg (this was a 16 year old who received a dose of 2.4 and survived through 3 years of follow-up). An analysis comparing patients with TNC doses above and below

the median dose of 16.5 x $10^7$ TNC/kg showed a trend toward improved survival at doses above the median, but the difference was not statistically significant (nominal log-rank p = 0.14).

### 6.2.10 Additional Efficacy Issues/Analyses

#### Published Reviews and Opinions

Krabbe disease is not mentioned explicitly in the 2005 IOM report on cord blood banking, although metabolic storage disorders are in the category for which the report considered allogeneic stem cell transplantation as "controversial; may be effective in selected patients." The Cochrane Collaboration has not reviewed the use of stem cell transplantation in Krabbe disease. The Prasad review in 2010 (Prasad and Kurtzberg 2010) reported UCB as standard of care, and cited the following as evidence: Escolar and Poe et al. 2005, Martin and Carter et al. 2006, and Prasad and Mendizabal et al. 2008. Search of the literature identified the follow additional primary report of experience with UCB in Krabbe disease: Duffner and Caviness, Jr. et al. 2009.

#### Published experience with UCB for Krabbe disease

*Escolar and Poe et al. 2005 (n=25)*
This is the article presenting the results of UCB transplantation discussed above in Section 6.2.4.

*Escolar and Poe et al. 2006*
The authors developed a 4-point staging system based on a categorization of specific clinical findings in order to predict post-transplant outcomes (predominantly cord blood). They found that patients with Stage 3 or 4 (moderate to severe neurologic involvement or advanced disease) had higher mortality or more severe disability following transplant, and they recommended that only patients in Stages 1 or 2 be considered for transplant.

*Martin and Carter et al. 2006 (n=16)*
This a report of 69 patients with lysosomal and peroxisomal storage disorders who received UCB transplantation under the COBLT study sponsored by NHLBI. Almost all (67) were transplanted at Duke. The populations included 16 patients with Krabbe disease, who are presumably a subset of the patients already considered in the review of the Docket datasets. The article does not provide efficacy information specifically for Krabbe disease patients. However, it did report on an analysis showing that, for the entire group, survival was not statistically significantly associated with age, cell dose, CD34+ dose, performance status, or HLA match number, but it was significantly worse for non-Caucasians and those who received units as part of an expanded access program.

*Prasad and Mendizabal et al. 2008 (n=36)*

This is a report of 159 patients who received UCB transplantation at Duke, including 36 patients with Krabbe disease. This appears to consist of patients whose data were also submitted to the Docket and therefore does not provide additional evidence regarding survival. Most results are presented for the study population as a whole. However, a graphic of Krabbe-specific survival data appeared very similar to that shown in Figure 10. The article does not state how the diagnosis of Krabbe disease was established and no comparisons to specific untreated Krabbe disease control data are provided.

*Duffner and Caviness, Jr. et al. 2009*

This is report of a workshop on outcome of presymptomatic infants transplanted for Krabbe disease. Abstracts presented at the workshop provided reports of follow-up. Although the type of stem cell transplantation is not identified, those reported from Duke were presumably all or mostly UCB. The publication is of note because it provides outcome information other than survival. Results are quoted below:

> Duke/UNC have evaluated 16 presymptomatic children transplanted at Duke and elsewhere for early infantile Krabbe disease. Of these, two have died in transplant. Of the remainder, all are spastic, although three are reported to be mild. Five require gastrostomies (although are able to eat by mouth), all are below the 3% for height and weight and most are below the 3% for head circumference. Receptive language is normal; however, all have abnormal expressive language because of impaired articulation. All have abnormal gross motor control, with 50% walking with assistive devices and only 25% able to walk independently. The investigators reported that all are considered to be normal cognitively. (There was a discussion at the meeting as to the difficulty in assessing intelligence accurately in children with such severe motor and language deficits.)
>
> A composite group of nine children from other PBMTC [Pediatric Bone Marrow Transplantation Consortium] transplant centers in the United States and Canada was also presented. … Six infants with a positive family history of early infantile Krabbe disease and low GALC activity were transplanted before symptom onset. One died of complications of transplant. Of the remaining five, all have delayed development and abnormal neurologic examinations. Three of the four children beyond 3 years of age are unable to walk without assistance because of slowly progressive spasticity. Three of four have acquired microcephaly, four of four have weights below the 3%, and three of four have heights <5%. Progressive neurological deterioration is present in three of four. (The child with stable, albeit delayed development, is only 3 years old.) (Duffner and Caviness, Jr. et al. 2009)

The discussion in Duffner and Jalal et al. 2009 is worth noting:

> Of concern in the age of bone marrow transplantation is that, even within families with the later-onset phenotype, there may be wide differences in presentation and course. Phelps et al. [14] [Phelps and Aicardi et al. 1991], for example, described two siblings, one of whom was confined to a wheelchair and institutionalized whereas her sibling remained neurologically normal despite comparable enzyme activity and computed tomography findings. Therefore, preemptively transplanting the sibling of an affected child with the same genetic abnormality may be unjustified. The situation becomes even more complex if newborns are screened for Krabbe disease at birth. Because neither the level of galactocerebrosidase activity nor the genetic mutation reliably predicts phenotype and there may be wide phenotypic variability even within families, the

decision on whether to recommend treatment is daunting [15]. Until we gain a better appreciation of the natural history of these later-onset phenotypes, decisions regarding aggressive treatment will necessarily be based on inadequate data.

In contrast, the decision regarding hematopoietic stem cell transplantation is more straightforward in the early infantile phenotype, which is known to have little clinical heterogeneity and there is the certain knowledge that, in the absence of transplantation, neurologic devastation and death are inevitable. Unfortunately, bone marrow transplantation is ineffective unless the child with the early infantile phenotype has the transplantation before developing symptoms. There is thus an urgent need for both physicians and families to be able to recognize the earliest signs and symptoms of the disease, as well as to be aware of the age at which these symptoms begin to manifest. (Duffner and Jalal et al. 2009)

*Reviewer's Comment:*
*The recommendation in the last paragraph is based on the findings described above in the publication (Escolar and Poe et al. 2005). The cautions expressed in the first paragraph may be applicable to the presymptomatic early infantile onset case as well, unless one has certainly that the asymptomatic patients actually would have developed the early infantile onset phenotype.*

*Evidence from published data regarding the effect of UCB on other aspects of Krabbe disease is limited by lack of objective comparisons to controls and by susceptibility to possible selection or reporting bias.*

*With the newborn screening taking place in New York, and maybe beginning in additional states, there could be an opportunity to develop evidence that could resolve the question: if a program of wholesale neonatal transplantation appears clearly to alter the population distribution of the phenotype, that might be regarded as evidence of an effect of UCB transplantation on the disease.*

## 6.3 X-Linked Adrenoleukodystrophy (ALD)

X-linked adrenoleukodystrophy (ALD) is an X-linked peroxisomal disorder cause by abnormal beta oxidation that results in accumulation of very long chain fatty acids (VLCFAs). The incidence is estimated be 1 in 100,000 to 1 in 20,000 (Moser 1997). The disease involves a mutation in the ATP-Binding Cassette, Subfamily D, Member 1 gene (ABCD1), which encodes a transporter important for moving VLCFAs into peroxisomes. VLCFAs accumulate in the affected organs, which are the CNS, adrenal cortex, and testes. The disease has been classified into a number of phenotypes, with a wide range in severity that may even vary dramatically within a family (Moser and Moser et al. 1991; Moser 1997; Moser and Loes et al. 2000). Neither mutation nor biochemistry predicts phenotype.

The childhood cerebral form usually presents in boys between 4 and 8 years, initially with behavior problems, then with neurologic deterioration including cognitive abnormalities, blindness, and quadriparesis. Once symptoms develop, progression is typically rapid, with total disability in 6 months to 2 years, and death in 5 to 10 years.

A milder form, adrenomyeloneuropathy (AMN) usually presents in young adult males as spinal cord dysfunction, but may present as progressive cerebellar disorder. An Addison-disease-only phenotype may be the expression in about 10% of patients. Carrier females can also have some mild manifestations of the disease.

There is no approved drug or biologic therapy for ALD. Lorenzo's oil has been studied in ALD, and is thought to be of some benefit in delaying progression in patients with early or mild disease (Moser and Moser et al. 2007).

### 6.3.1 Methods

Efficacy was evaluated by computing estimates for post-transplant survival obtained from pooling the three datasets described in Section 5.1. Results were compared to historical control survival data obtained from the literature. The literature was reviewed for additional reports of experience with unrelated cord blood use in ALD.

In the Docket datasets, diagnostic information other than the diagnosis of ALD was not provided. Thus, eligibility criteria for the series and the criteria for classification of the phenotype are unknown. Although the Lansky scores recorded in the Duke dataset give some indication of patient status, there is not an explicit representation of whether or not a patient had neurologic symptoms at the time of UCB transplantation. Information on disease-specific outcomes that might have been of interest, such as neurologic findings, was not provided. A slight majority (52%) of the cases came from the Duke dataset. As noted in Section 5.1, there are questions about the accuracy of the follow-up times for censored observation in that dataset.

### 6.3.2 Demographics

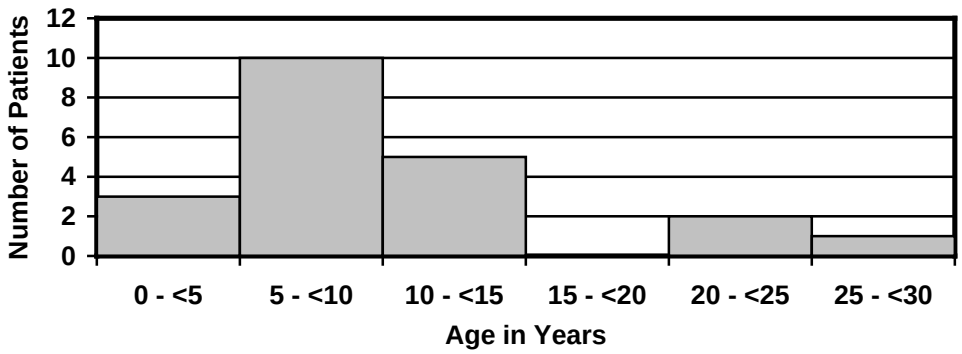
Basic demographics for the ALD patients in the pooled datasets are shown below, together with basic treatment data. Demographic information other than age was not provided in the NYBC dataset.

**Table 12: Demographics and Treatment Data for Patients with ALD – Docket Data**

| | |
|---|---|
| Total N | 21 |
| Age in Years Mean (SD) | |
| Mean (SD) | 10.0 (6.5) |
| Median (Range) | 8.2 (2.4 – 26.3) |
| Gender | |
| Male | 67% (14) |
| Unknown (presumed male) | 33% (7) |
| Race | |
| Caucasian | 52% (11) |
| Asian | 10% (2) |
| African/American | 5% (1) |
| Hispanic | 5% (1) |
| Unknown | 29% (6) |
| Dosing ($x10^7$ TNC/kg prefreeze) | |
| Median | 4.0 |
| $10^{th}$, $25^{th}$, & $75^{th}$ percentiles | 1.7, 2.6, 7.8 |
| Dose < 2.5 | 24% (5) |
| HLA Match | |
| 6/6 | 14% (3) |
| 5/6 | 38% (8) |
| 4/6 | 48% (10) |
| Data source | |
| Duke[1] | 52% (13) |
| NMDP[2] | 10% (2) |
| NYBC[2] | 29% (6) |

[1] Duke count includes one case each also reported by NMDP and NYBC
[2] Excludes cases also reported by Duke

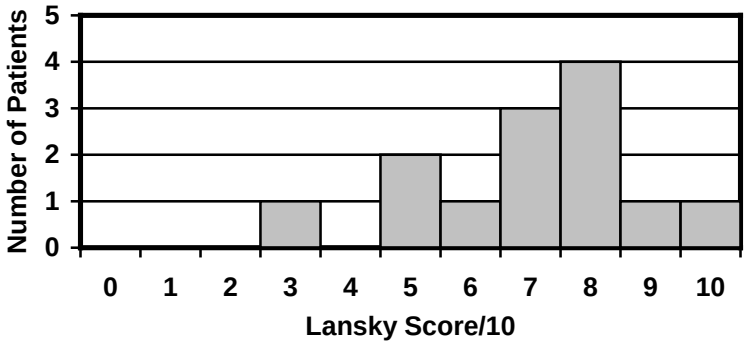
**Figure 15: Age Distribution for ALD Patients – Docket Data**




The presence of three patients who were 20 years or older raises some concern about the accuracy of the reporting of the diagnosis, and whether these might be more appropriately classified as AMN.

The Lansky score is a general play-performance score described above in Section 6.1.2. The score was recorded only in the Duke dataset. Except for one patient with a score of 30 (in bed, needs assistance for quiet play), the scores ranged from 50 (gets dressed but lies around much of the day) to 100 (fully active). These scores indicate there was a fairly broad range in clinical status at the time of transplant.

**Figure 16: Lansky Score Distribution of Pooled Docket ALD Patients**




(Lansky scores were available only for the 13 patients in Duke dataset.)

### 6.3.3 Subject Disposition

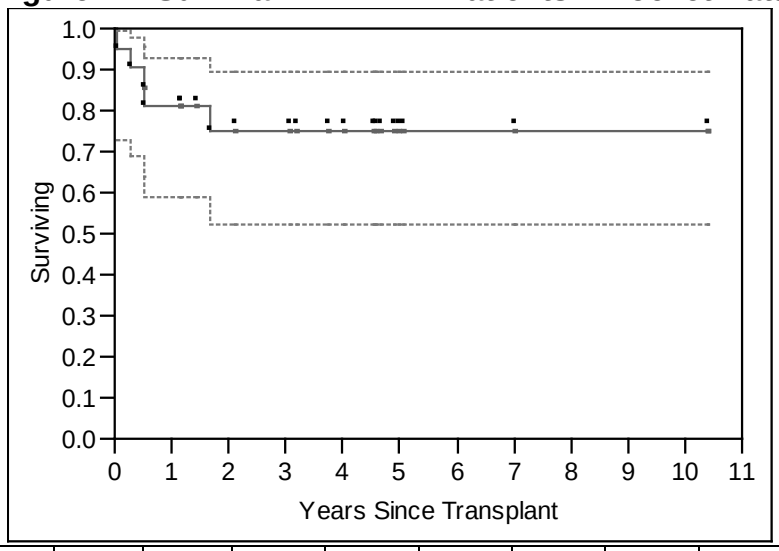
No protocol was provided for this study, and there is no information available about screening, eligibility criteria, or diagnostic criteria. Of the 21 ALD patients, 5 are reported to have died. Two deaths were attributed to neurologic deterioration or progression of ALD, and there was one death each attributed to GVHD, veno-occlusive disease, and pneumonia. (One patient in the Duke dataset had a cause of death listed as infection, but the patient was not reported to have died – for purposes of the analysis the patient was treated as survived, under the assumption that the infection was a misplaced non-fatal event.)

### 6.3.4 Analysis of Primary Endpoint(s)

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown in Figure 17 below for the 21 ALD patients from the Docket datasets. There is 19% mortality by the end of the first year. The estimated fraction surviving at 5 years is 75% with a lower confidence limit of 52%, but the number at risk is very low at 5 years and beyond.

**Figure 17: Survival in 21 ALD Patients – Docket Data**

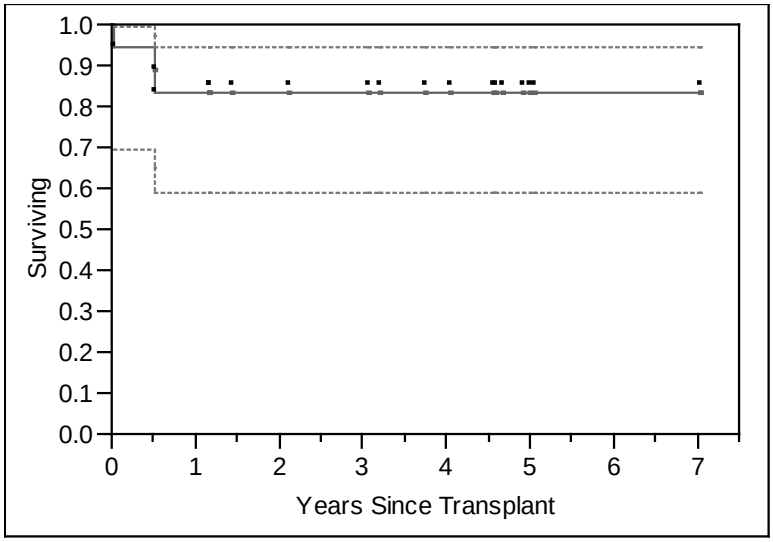



| Year | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Survival | 1.00 | 0.81 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 |
| No. at Risk | 21 | 17 | 13 | 12 | 9 | 3 | 2 | 2 | 1 | 1 | 1 |

The longest survival, censored at 10.4 years following transplant, was seen in the 26 year old patient, the second longest, censored at 7.0 years following transplant, was seen in a 9 year old. Survival at 5 years and beyond came only from the Duke dataset, for which is there is concern about the validity of the follow-up times reported for censored observations.

The three patients older than 20 were not typical for the childhood cerebral phenotype, so an additional analysis was done for only the 18 patients 14 years and younger, as shown in Figure 18:

**Figure 18: Survival in 18 ALD Patients ≤ 14 Years – Docket Data**

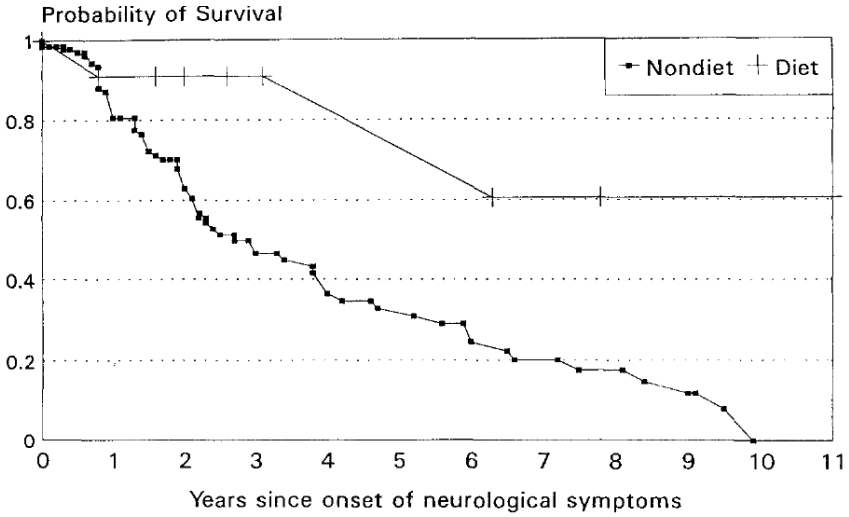



Although the estimated survival probabilities are somewhat higher, there is no demonstrably different experience in this younger subgroup than in the group as a whole.

## Historical Experience

Historical data are available from a number of sources. One of the earliest substantial reports that provided a survival analysis came from a review of cases from the files at Johns Hopkins University (Moser 1995). The population consisted of 139 patients with the childhood cerebral phenotype who had not received Lorenzo's oil (the "Nondiet" group in Figure 19). The analysis showed progressive failure over a course of 10 years following the onset of neurologic symptoms. The 5-year survival was about 30%.

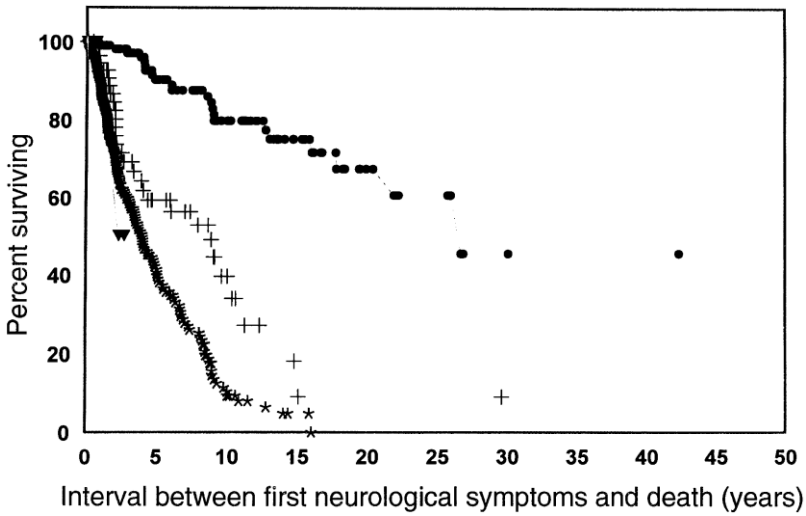
**Figure 19: Survival Following Onset of Neurologic Symptoms in 139 Untreated ALD Patients – Moser 1995**




Probability of survival from onset of neurologic symptoms to death. Untreated [Nondiet] (n=139) and treated [Diet] (n=11) symptomatic adrenoleukodystrophy patients.
Source: Moser 1995

In a subsequent publication, Moser presented a larger series of 257 patients with the childhood cerebral phenotype along with data on other phenotypes (Moser 1997). However, the source and selection of these data are not made clear in the publication. It is difficult to estimate from the graph in the publication (see Figure 20), but the 5-year survival in the childhood cerebral form appears to be approximately 40%.

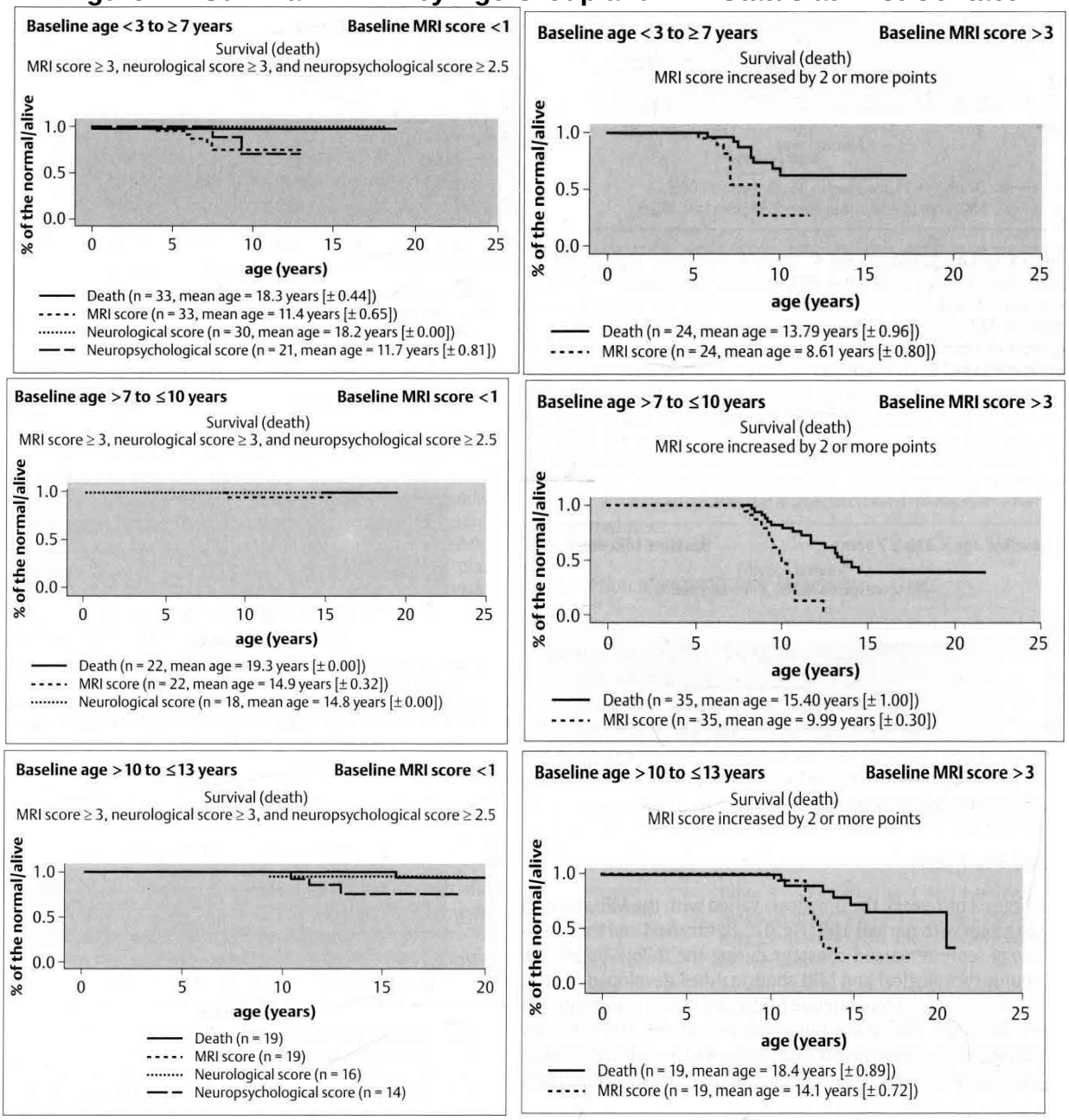
**Figure 20: Survival Following Onset of Neurologic Symptoms in ALD Patients – Moser 1997**




Survival from time of first neurological symptom (untreated males only). Note the rapid rate of progression of cerebral forms irrespective of age at onset. Filled circles = AMN (*n* =116); filled triangles = adult cerebral (*n* = 3); plus signs = adolescent cerebral (*n* = 60); asterisks = childhood cerebral (*n* = 257).
Source: Moser 1997

In a review of 372 cases from the records at the Kennedy Krieger Institute at Johns Hopkins, Moser undertook an extensive analysis of survival looking at the effect of age and MRI findings on prognosis (Moser and Loes et al. 2000). In that population, 8% had received BMT. Post-transplant data were excluded from the analysis. Selected graphics from that publication covering the age range of 3 to 13 years are shown in Figure 21 below. Those graphics are reproduced here because they exhibit the overall survival experience, as indicated by the solid lines. (The graphics also include information on other endpoints, but these are not considered further here because no comparable endpoints were included in the Docket datasets.)

**Figure 21: Survival in ALD by Age Group and MRI Status at First Contact**




Left graphs: survival (solid lines) in designated age groups and with normal MRI at first contact.
Right graphs: survival (solid lines) in designated age groups who had moderate to severe abnormality on MRI at first contact.
Analyses exclude post-transplant experience.
[Notes: Times to progression of MRI, neurologic, and neuropsychiatric scores are also plotted but are not considered further here. Age group labels for the two top graphs appear to have a typographic error, and should instead read ">3 to ≤ 7 years."]
Source: Moser and Loes et al. 2000

Most recently, Mahmood presented survival curves for a series of 283 boys with childhood cerebral ALD from the Kennedy Krieger Institute who had not received HSCT (Mahmood and Raymond et al. 2007). For that group, the 5-year survival after onset of symptoms was 66%. He also presented an analysis of survival for 19 patients who received HSCT compared with a group of 30 non-transplanted patients with similar MRI scores. For the subset of 30 patients with early stage disease, the 5-year survival after first abnormal MRI was 54%.

**Figure 22: Survival from Onset of Symptoms in ALD – Mahmood 2007**

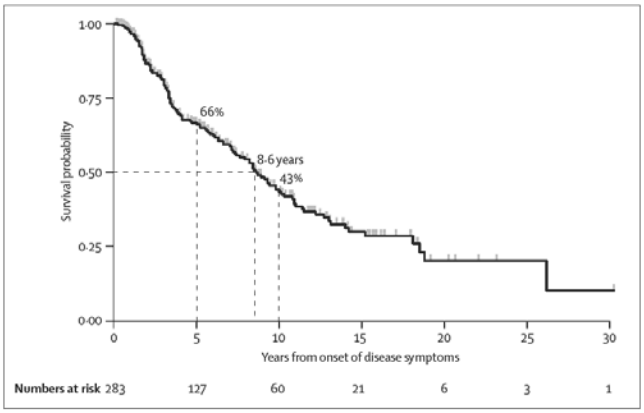



*Figure 2:* Kaplan-Meier estimate of survival for 283 boys with childhood cerebral X-linked adrenoleukodystrophy after development of neurological symptoms (cognitive, behavioural, or neurological symptoms)

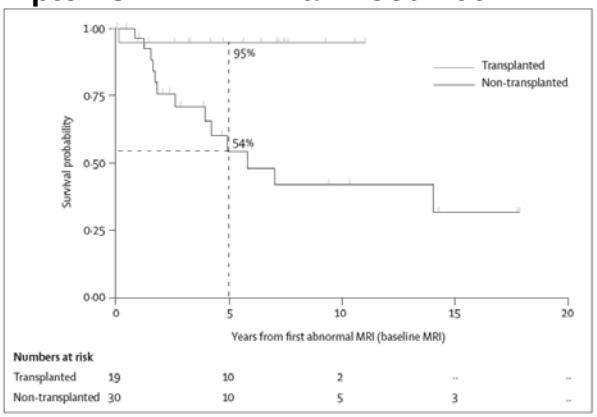



*Figure 4:* Kaplan-Meier estimates of survival for 19 transplanted patients with early stage cerebral adrenoleukodystrophy and for 30 non-transplanted patients with early stage cerebral adrenoleukodystrophy (ie, neurological deficit score of 0 or 1 and MRI severity score less than 9) Survival was different in these two groups ($\chi^2$=7·47, p=0·006).

Source: Mahmood and Raymond et al. 2007

*Reviewer's Comments:*
*The ALD phenotype is variable, and without knowledge of the timing of onset of symptoms and degree of MRI abnormalities in the Docket population, it is difficult to identify an appropriate external control.*

*The lower limit of the estimated 5-year survival from the Docket dataset is about 52% (Figure 17), so that the confidence interval does not exclude the estimated 5-year survival of 66% following onset of symptoms (Figure 22, left display) or 54% following first MRI abnormality in early disease (Figure 22, right display) from the most recently published historical experience. While there is some suggestion that overall survival following UCB transplantation for patients in the database is better than that of patients who have had onset of neurologic symptoms in some of the older series, survival following UCB transplantation appears to be worse than survival in diagnosed patients who have not developed MRI abnormalities (Figure 21, left displays). Although the recent analysis by Mahmood estimated higher survival in patients who underwent HSCT compared to no HSCT (Figure 22, right display), the UCB survival outcomes from the docket datasets are not that similar to those report by Mahmood for HSCT; in fact, for the first few years where the follow-*

*up experience is more complete, the UCB results seem closer to those of the untreated group.*

### 6.3.5 Analysis of Secondary Endpoint(s)

The potential to substantiate claims for clinical benefits other than survival was not evaluated because no disease-specific outcome data were included in the Docket datasets.

### 6.3.7 Subpopulations

Of the 21 patients with ALD, gender was not recorded for 7 (33%), but all can be presumed to be male. Race was not recorded for 6 (29%).

By proportional hazards analysis, neither age nor race appeared to be related to survival outcome, either in univariate analyses, or in a multivariate analysis (n = 15) incorporating age, race, and dose ($p = 0.51$ for age, $p = 0.27$ for race, and $p = 0.16$ for dose in the multivariate analysis).

### 6.3.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A univariate proportional hazards model found no statistically significant relationship between dose (as prefreeze TNC/kg) and survival (nominal $p = 0.86$) with an estimated 2.2% *increase* in hazard for each increase in dose of $10^7$ TNC/kg. There were only 5 patients with a dose < $2.5 \times 10^7$ TNC/kg. There was one death in that subset, and the survival curve appeared similar to that of those who got the higher doses. An analysis comparing patients with TNC doses above and below the median dose of $4.0 \times 10^7$ TNC/kg showed a slight trend toward worse early survival, but with improved late survival, for doses above the median, but the difference was not statistically significant (nominal log-rank $p = 0.14$).

### 6.3.10 Additional Efficacy Issues/Analyses

<u>Published Reviews and Opinions</u>

Neither the review of cord blood banking by an AAP Work Group nor the 2005 IOM report commented explicitly on the effectiveness of UCB for ALD, but they both categorized stem cell transplantation for metabolic storage disorders as “controversial; may be effective in selected patients.” A 2010 review by Prasad (Prasad and Kurtzberg 2010) regarded UCB as standard of care for adrenoleukodystrophy, and cited the following sources as evidence: Martin and Carter et al. 2006, Beam and Poe et al. 2007, and Prasad and Mendizabal et al. 2008. The Cochrane Collaboration has not reviewed the use of stem cell transplantation in ALD.

## Published experience with UCB in ALD

*Martin and Carter et al. 2006*

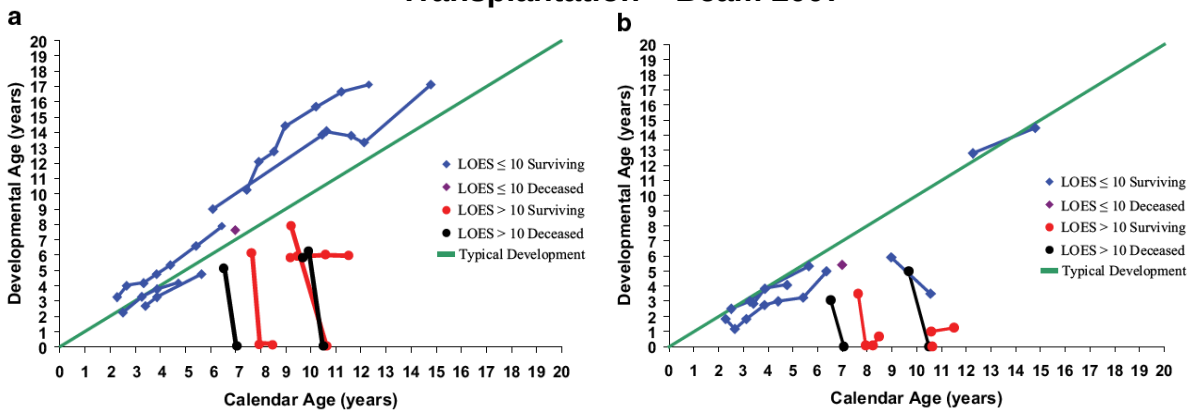
This a report of 69 patients with lysosomal and peroxisomal storage disorders who received UCB transplantation under the COBLT study sponsored by NHLBI. Almost all (67) were transplanted at Duke. The populations included 8 patients with adrenoleukodystrophy. The report presents summaries of engraftment, survival, toxicity, and GVHD, but results are not broken down by disease. For the entire group, survival was 80% at 6 months and 72% at one year. Survival was not statistically significantly associated with age, cell dose, CD34+ dose, performance status, or HLA match number, but it was significantly worse for non-Caucasians and those who received units as part of an expanded access program. The article does not provide efficacy information specifically for ALD patients.

*Beam and Poe et al. 2007*

This reports on a retrospective analysis of 12 patients with ALD referred to Duke for transplantation. This presumably consists of patients whose data were also included in the Docket submission, so it does not provide additional survival information. Median follow-up was 3.3 years; survival past 6.25 months was 67% (95% CI: 40% – 93%), which is slightly lower than, but consistent with, the experience shown in Figure 17. The report noted that one patient died after starting conditioning and did not receive transplant. The death was attributed to “shock and brain herniation likely secondary to adrenal crisis.”

From an analysis aimed at determining whether baseline observations predicted outcome after cord blood transplantation, the authors found that pretreatment MRI-based Loes score correlated with post-transplant cognitive and motor development, but baseline neurophysiologic studies were not predictive. A graphic from the article is reproduced below as Figure 23 (colors referenced in the caption refer to the graphic as originally published):

**Figure 23: Cognitive and Gross Motor Development in ALD Following UCB Transplantation – Beam 2007**




(a) Cognitive development and pretransplant MRI Loes scores. The green line [long diagonal] represents typical development. Each blue line [diamonds] represents the longitudinal cognitive course of a surviving patient with baseline Loes Scores <10. The red lines [circles] represent the longitudinal cognitive course of surviving patients with Loes Scores >10. The black and purple represent deceased patients.
(b) Gross motor development and pretransplant MRI Loes scores. The green line [long diagonal] represents typical development. Each blue line [diamonds] represents the longitudinal motor course of a surviving patient with baseline Loes scores >10. The red lines [circles] represent the longitudinal motor course of surviving patients with Loes scores <10. The black and purple represent deceased patients. Note that motor scores are in general lower than cognitive scores in (a).
Source: Beam and Poe et al. 2007

The article did not provide control cognitive and gross motor data from an untransplanted ALD population for comparison.

*Reviewer's Comments:*
*This report is on patients transplanted at Duke, but there are some noteworthy differences between the data reported in this article and the Duke dataset. The Duke dataset contains two patients older than 20; they were not included in the article. The article reports that one of the 12 patients died after beginning conditioning and did not get transplanted; that patient does not appear in the Duke dataset. Further, the follow-up times reported in the article exactly match those in the Duke dataset if the Excel "NOW()" function is replaced by the date 8/1/2006. This is evidence that the follow-up times used in the article have the same data quality issue as identified for the Duke dataset (see* Dataset Integrity and Quality*, in Section 3.1).*

*By the nature of the population studied, this analysis did not address prediction of disease course in patients who were not transplanted, but the finding that MRI is predictive of outcome is generally in accord with a similar finding in untreated patients, as indicated by Figure 21.*

*Prasad and Mendizabal et al. 2008*

This is a report of 159 patients who received UCB transplantation at Duke, including 13 patients with adrenoleukodystrophy. This appears to be comprised of patients whose data were also submitted to the Docket, and therefore does not provide additional evidence regarding survival. The article does not state how the diagnosis of ALD was established and does not identify patients' clinical status at time of transplant. Most results are presented for the study population as a whole. However, the ALD-specific data showed a 69% survival through 2 years and extending to 10 years, based on a median follow-up of 3.1 years. The survival is slightly lower than, but consistent with, the experience shown in Figure 17. The rate of engraftment with high (>90%) donor chimerism was 85%. No comparisons to untreated ALD control data were provided.

*Reviewer's Comment:*
*Evidence from published data regarding the effect of UCB on aspects of ALD other than survival is limited by lack of objective comparisons to controls and susceptibility to possible selection or reporting bias.*

## 6.4 Primary Immunodeficiency Diseases – Severe Combined Immunodeficiency (SCID)

Primary immunodeficiency diseases are a heterogeneous collection of congenital disorders of immune function. Even Severe Combined Immunodeficiency (SCID) is a collection of different entities. Many of the various individual primary immunodeficiency disorders are represented by a very small number of cases in the pooled Docket datasets. The clear predominant subcategory was the SCID syndrome(s).

SCID is caused by mutation in various genes involved in lymphocyte development and function. The incidence is estimated to be between 1 in 50,000 to 500,000 live births. The gene defect is unknown in about 14% of cases. Of the known gene defects, only one causes an X-linked syndrome, but about half of all SCID cases are X-linked.

Children affected with SCID usually present in the first year of life with recurrent infections and failure to thrive. T cell counts are very low, the thymic shadow is small or absent, hypogammaglobulinemia is common, and various tests of immune function are abnormal. Diagnostic criteria are: lymphocyte count < 300/$mm^3$, less than 20% T cells, and mitogen response < 10% of control. Presence of maternal T cells in the circulation is also diagnostic. If uncorrected, SCID is usually fatal in the first year of life. Omenn syndrome, in which T cells may be present but function is abnormal, is included under the SCID umbrella for purposes of this review.

The only approved specific therapy for SCID is Adagen (PEG-ADA, pegademase bovine), which is effective for the subset of patients in whom SCID is due to adenosine deaminase deficiency. IVIG is an approved therapy for a variety of primary immunodeficiency disorders.

### 6.4.1 Methods

Efficacy was evaluated by computing estimates for post-transplant survival obtained from pooling the three datasets described in Section 5.1. Results were compared to historical control survival data obtained from the literature. Review of a reasonably well documented case report in the Docket was also contributory.

In the Docket datasets, diagnostic information other than the diagnosis of SCID was not provided; however, the NMDP dataset did identify subtypes of SCID. Eligibility criteria for the series and the criteria for classification of the phenotype are unknown. Information on disease-specific outcomes other than survival that might have been of interest, such as immune function evaluation or infection history, were not provided in the datasets. The Docket included one case report that did provide some additional clinical data other than survival.

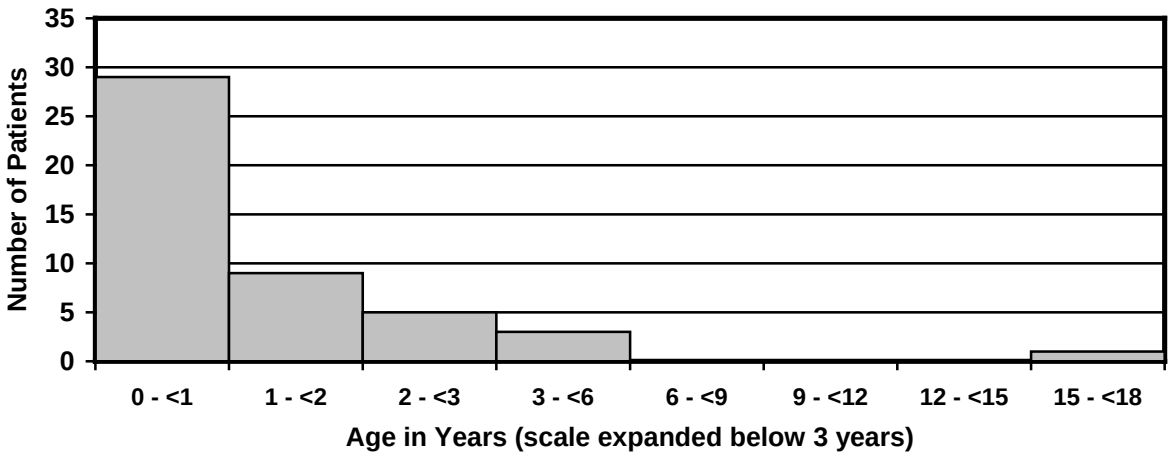
### 6.4.2 Demographics

The case report is described in a subsequent section. Basic demographic information for the SCID syndrome patients in pooled datasets are shown below, together with basic treatment data. Demographic information other than age was not provided in the NYBC dataset.

**Table 13: Demographics and Treatment Data for SCID Patients – Docket Data**

| | |
|---|---|
| Total N | 47 |
| Age in Years | |
| Mean (SD) | 1.2 (25) |
| Median (Range) | 0.6 (0 – 17) |
| Gender | |
| Male | 36% (17) |
| Female | 11% (5) |
| Unknown | 53% (25) |
| Race | |
| Caucasian | 43% (20) |
| African/American | 2% (1) |
| Asian | 2% (1) |
| Unknown | 53% (25) |
| Dosing (TNCx$10^7$/kg prefreeze) | |
| Median | 12.7 |
| $10^{th}$, $25^{th}$, & $75^{th}$ percentiles | 6.5, 8.5, 20.3 |
| Dose < 2.5 | 0% (0) |
| HLA Match | |
| 6/6 | 15% (7) |
| 5/6 | 36% (17) |
| 4/5 | 40% (19) |
| 3/6 | 4% (2) |
| 2/6 | 2% (1) |
| Unknown | 2% (1) |
| Data source | |
| NMDP | 47% (22) |
| NYBC | 53% (25) |

**Figure 24: Age Distribution for SCID Patients – Docket Data**




While a breakdown of ages below one year would be desirable, most of the cases came from the NYBC database, which reported age in years only as whole numbers. The presence in the dataset of 9 patients who are 2 years or older is not expected for patients with the usual presentation of SCID. The presence of a 17 year old with SCID in the NYBC dataset is difficult to understand unless it represents a data entry error or a second transplant for a patient initially transplanted in childhood.

### 6.4.3 Subject Disposition

No protocol was provided for this study, and there is no information available about screening, eligibility criteria, or diagnostic criteria. Of the 47 total SCID patients, 16 are reported to have died. The causes of death are tabulated below:

**Table 14: Cause of Death in SCID Patients – Docket Data**

| | N |
|---|---|
| Respiratory | 8 |
| Infection | 3 |
| Misc.* | 5 |

* Pulmonary embolism-1, cardiotoxicity-1, “HemolAnCard”-1, other, unspecified-2

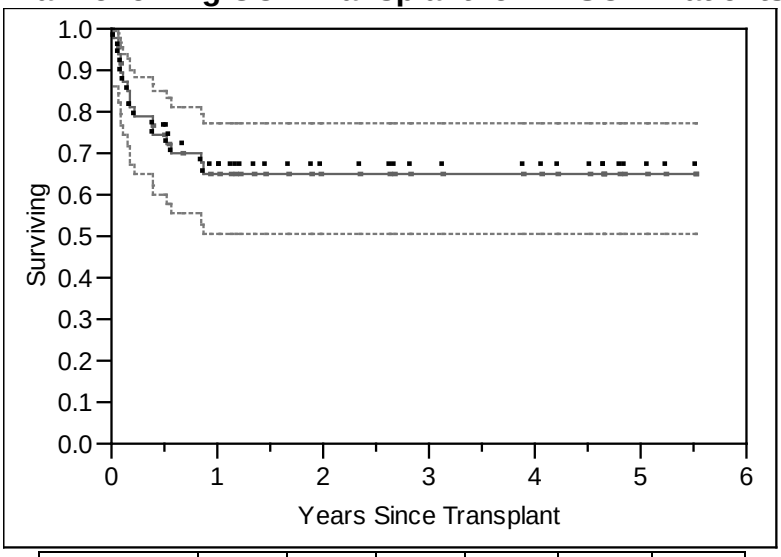
Three patients received a second transplant due to engraftment failure (one of these subsequently died). A fourth patient received a second transplant after 19 months for an unspecified reason.

### 6.4.4 Analysis of Primary Endpoint(s)

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown below for the 47 SCID patients from the Docket datasets. There is about 35% mortality by the end of the first year, but mortality is low thereafter. Median follow-up was 1.1 years; the 75th quartile of follow-up was 3.1 years.

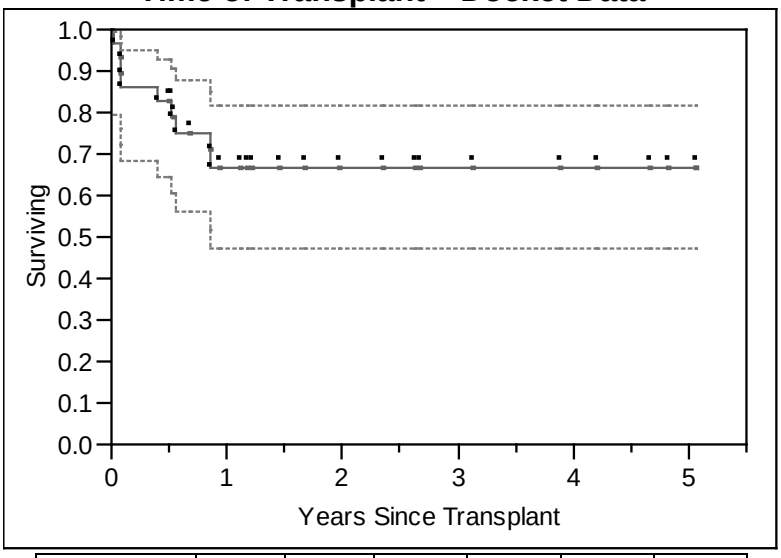
**Figure 25: Survival Following UCB Transplant for 47 SCID Patients – Docket Data**




| Year | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Survival | 1.00 | 0.65 | 0.65 | 0.65 | 0.65 | 0.65 |
| No. at Risk | 47 | 26 | 16 | 12 | 10 | 3 |

Since the presence of patients 2 years and older raises questions about the accuracy of the SCID diagnosis for those patients, an analysis of survival was performed for only the 29 patients under 1 year of age. Results were generally similar, as shown in Figure 26:

**Figure 26: Survival Following UCB Transplant for 29 SCID Patients < 1 Year Old at Time of Transplant – Docket Data**



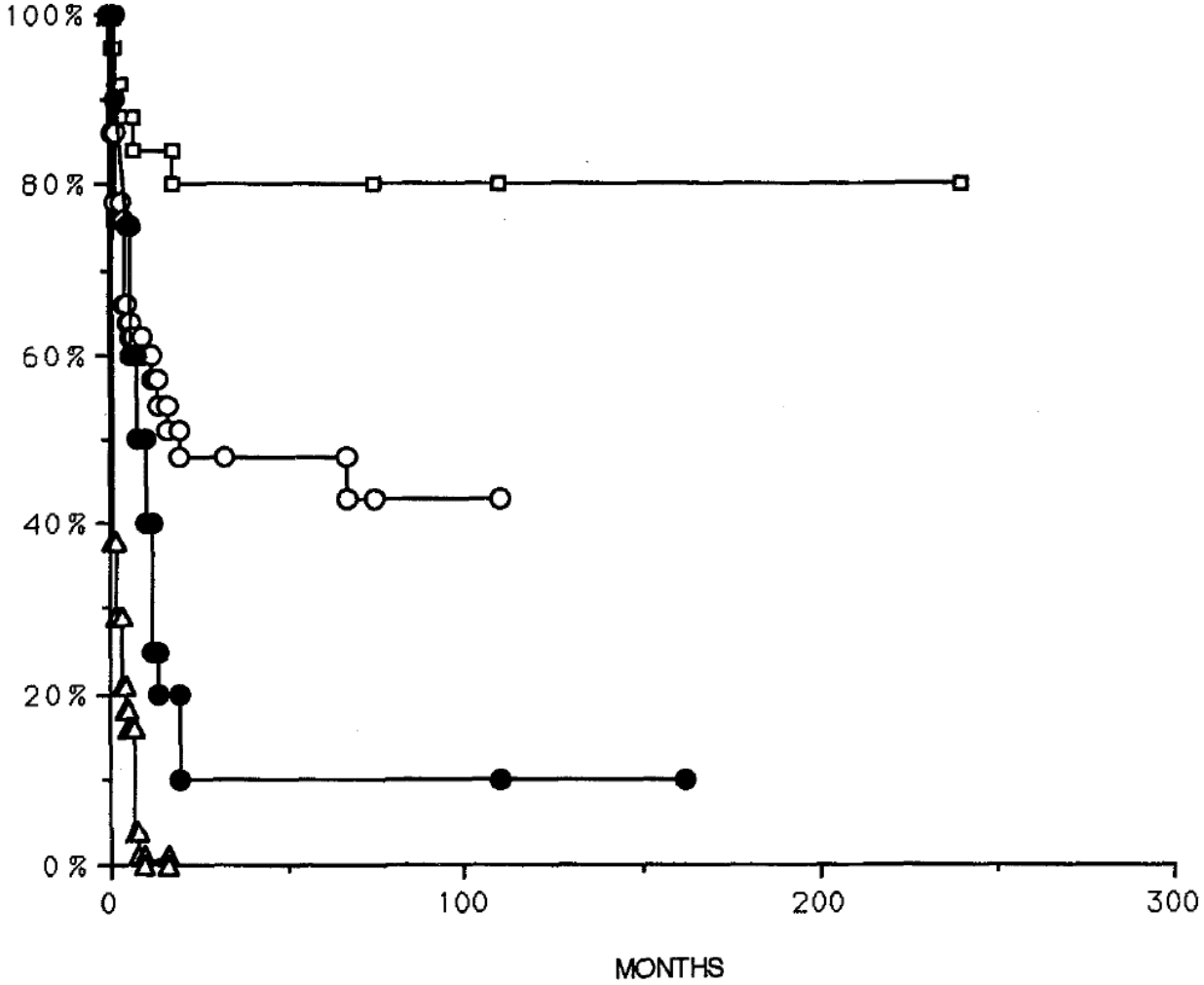

| Year | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Survival | 1.00 | 0.67 | 0.67 | 0.67 | 0.67 | 0.67 |
| No. at Risk | 29 | 15 | 9 | 6 | 4 | 1 |

## Historical Experience

A case series of 434 cases published by Hitzig (Hitzig and Kenny 1978) reported that "All untreated infants died within the first months of life." The article does not identify how may patients were treated or how (although transplants were being performed by that time), but the article does report on 244 autopsies. If one takes 244 as a representation of the untreated cases, then for an observed survival rate of 0 out of 244, the upper 2.5% confidence limit for the survival probability is 0.015, and even if it is allowed that 1 may have survived the upper confidence limit would be 0.023.

A series of 22 patients who did not undergo HSCT was reported by Stephan (Stephan and Vlekova et al. 1993) from a series of 117 cases referred to a Paris hospital between 1970 and 1992. Individual data were not provided in the report, but the graphic (Figure 27) indicates all non-transplanted patients died by about 18 months. Thus, the 2.5% upper confidence limit for the probability of survival past 18 months is 0.154.

**Figure 27: Survival in SCID by BMT Type and Without Transplant – Stephan 1993**




Survival curves of 117 patients with SCID according to transplantation procedure. Thirty patients received HLA-identical transplants *(clear squares),* with median follow-up of 129 months; 50 patients received T cell-depleted HLA-non-identical transplants *(clear circles),* with median follow-up of 34 months; 10 patients received fetal liver transplants *(dark circles),* with median follow-up of 148 months, and 22 patients did not undergo transplantation *(clear triangles).*
Source: Stephan and Vlekova et al. 1993

*Reviewer's Comments:*
*The lower limit of the confidence interval for survival at 2 years from the Docket data, at about 50%, appears to be well above the survival experience from the historical control. Further, from a sensitivity analysis under the rather conservative assumption that censored events were all actually deaths, the 9 survivors at 2 years, out of 29 UCB treated SCID patients under 1 year of age, differs with nominal p < 0.00001 from the experience of no survivors out of the 266 combined cases reported by Hitzig (using only 244 autopsy cases) and Stephan. The nominal significance would still be p < 0.0013 in the more extreme sensitivity scenario assuming the*

*historical rate were 7.5%, or assuming that there were only 7 survivors in the UCB transplant cases and that the 2-year survival rate for the historical controls were as high as 5%. The statistical significance is even greater using the entire experience in the 47 patients.*

*Adagen (pegademase bovine) has been an available therapy since 1990 for patients with SCID due to ADA deficiency. SCID subtypes were only identified in the NMDP dataset, and 2 of those 22 patients were listed as "SCIDAD." For the 20 other patients, estimated survival at 2 years post-transplant was 73% with the lower end of the 95% CI at about 48%, and 9 of the patients were known to have lived to at least age 2 years. Thus, it does not appear the improved survival in SCID after UCB can be explained simply by the availability of Adagen.*

Case Report

The case report was provided in Docket document 2006-D-0157-DRAFT-0078. It is a published report (Jaing and Lee et al. 2006) of an infant with SCID who received unrelated UCB transplantation at just over 5 months of age.

The male infant was admitted at 5 months of age with a diagnosis of SCID. He had hypogammaglobulinemia and lymphopenia, with T cell count of 6/$mm^3$ and B cell count of 291/$mm^3$. He had a mutation of the IL-2 common $\gamma$-chain. His medical history included E. coli UTI at 3 months and oral candidiasis at 4 months. On admission he had P. carinii pneumonia and evidence of disseminated BCG disease (he had been vaccinated at 3 days of age). He received UCB transplant with 2 mismatches at a dose of $3.5 \times 10^7$ nucleated cells/kg and $3 \times 10^5$ CD34 cells/kg. Following transplant he had 20-30% donor chimerism, increased lymphocyte counts of 819 T cells/$mm^3$ and 228 B cells/$mm^3$, and normal immune responses. He had acute grade I GVHD involving the skin that responded to topical steroids. At 14 months post-transplant, he was reported in "very good clinical condition without medications."

The report of all deaths "within the first months of life" for untreated patients reviewed by Hitzig (Hitzig and Kenny 1978) was mentioned above. While it did not provide specific data, both that experience and that of Stephan (Stephan and Vlekova et al. 1993) appear to be highly incompatible with any patient being in "very good clinical condition without medication" at 14 months of age.

### 6.4.5 Analysis of Secondary Endpoint(s)

The potential to substantiate claims for clinical benefits other than survival was not evaluated because no disease-specific outcome data were included in the Docket datasets. The case report reviewed above included information on immune status, but that cannot be directly corroborated with the Docket datasets.

### 6.4.7 Subpopulations

Of the 47 patients with SCID, gender and race data were not recorded for 25 (53%).

Although a univariate proportional hazards model identified a borderline significant relationship between age and survival (p = 0.053), no relationship (p = 0.48) was seen when excluding the patient with age coded as 17 years. In light of the questionable nature of the reported age, that patient was excluded for any subpopulation analyses involving age.

By proportional hazards analysis, none of the variables age (teenager excluded), gender, or race appeared to be related to survival outcome, either in univariate analyses, or in a multivariate analysis (n = 22) incorporating age, gender, race, and dose (p = 0.32 for age, p = 0.38 for gender, p = 0.51 for race, and p = 0.95 for dose in the multivariate analysis).

### 6.4.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A univariate proportional hazards model found no significant relationship between dose (as prefreeze TNC/kg) and survival (nominal p = 0.33) with an estimated 1.9% decrease in hazard for each increase of $10^7$ TNC/kg. The relationship was slightly weaker with adjustment for age (teenager excluded). There was no patient with a dose < 2.5 x $10^7$ TNC/kg. An analysis comparing patients with TNC doses above and below the median dose of 12.7 x $10^7$ TNC/kg showed a trend toward improved survival for doses above the median, but the difference was not statistically significant (nominal log-rank p = 0.28).

### 6.4.10 Additional Efficacy Issues/Analyses

#### Published Reviews and Opinions

In a review of cord blood banking by an AAP Work Group (Work Group on Cord Blood Banking 1999), the summary of indications for allogeneic stem cell transplantation included “immune deficiency (e.g., severe combined immunodeficiency disease)” in the category of “effective.” Those conclusions were reflected in the 2005 IOM report on cord blood (Meyer and Hanna et al., 2005). The AAP review did not provide references to specific data in support of its determination, and the IOM report referenced studies in mice. The Cochrane Collaboration has not reviewed the use of stem cell transplantation in SCID.

A more recent review addressing the use of cord blood in SCID is found in Gennery and Cant 2007. The authors aggregated reports from several small case series and found a 77% survival in 30 SCID patients treated with UCB. The authors regarded the place of UCB in treating primary immunodeficiency disease as being well established.

## 6.5 Bone Marrow Failure – Fanconi Anemia (FA)

Fanconi anemia (FA) is a mostly autosomal recessive genetic disorder. Multiple genes have been associated with FA. The disease is subtyped into complementation groups depending on the gene involved. Primary clinical features include anemia and eventual bone marrow failure. Patients also have limb and organ malformations and are at increased risk for leukemia and other neoplasms. The common mechanistic feature is defective production of a multiprotein complex that has a role in a pathway involved in DNA repair. Diagnosis is made on the basis of a test for abnormal cellular response to DNA damage. Based on data from an international registry (Auerbach 2009), hematologic abnormalities manifest at a median age of 7 years, and the incidence of bone marrow failure rises over time, reaching 90% by age 40.

There is no approved drug or biologic therapy for Fanconi anemia.

### 6.5.1 Methods

Efficacy was evaluated by computing estimates for post-transplant survival obtained from pooling the three datasets described in Section 5.1. Results were compared to historical control survival data obtained from the literature. The literature was reviewed for additional reports of experience with unrelated cord blood use in FA.

In the Docket datasets, diagnostic information other than the diagnosis of Fanconi anemia was not provided. Thus, eligibility criteria for the series and the criteria for classification of the phenotype are unknown. There was no explicit representation of a patient's hematologic status at the time of UCB transplantation. Information on disease-specific outcomes that might have been of interest, such as blood counts or bone marrow analysis, was not provided.

### 6.5.2 Demographics

Basic demographics for the FA patients in pooled datasets are shown below, together with basic treatment data. Demographic information other than age was not provided in the NYBC dataset, from which most of the cases came.

**Table 15: Demographics and Treatment Data for Patients with Fanconi Anemia – Docket Data**

| | |
|---|---|
| Total N | 39 |
| Age in Years | |
| Mean (SD) | 8.3 (3.2) |
| Median (Range) | 8 (3 – 15) |
| Gender | |
| Male | 5% (2) |
| Female | 18% (7) |
| Unknown | 77% (30) |
| Race | |
| Caucasian | 15% (6) |
| African/African-American | 3% (1) |
| Hispanic | 3% (1) |
| Unknown | 79% (31) |
| Dosing (TNCx$10^7$/kg prefreeze) | |
| Median | 4.5 |
| $10^{th}$, $25^{th}$, & $75^{th}$ percentiles | 1.3, 2.8, 7.6 |
| Dose < 2.5 | 23% (9) |
| HLA Match | |
| 6/6 | 15% (6) |
| 5/6 | 31% (12) |
| 4/5 | 44% (17) |
| 3/6 | 8% (3) |
| Unknown | 3% (1) |
| Data source | |
| NMDP | 23% (9) |
| NYBC | 77% (30) |

**Figure 28: Age Distribution of Fanconi Anemia Patients – Docket Data**

### 6.5.3 Subject Disposition

Of the 39 total patients with Fanconi anemia, 28 are reported to have died. The causes of death are listed in the table below:

**Table 16: Causes of Death in Fanconi Anemia Patients – Docket Data**

| | N |
|---|---|
| Infection | 13 |
| Pulmonary disease | 5 |
| Acute GVHD | 2 |
| Veno-occlusive disease | 2 |
| Multi-organ failure | 2 |
| GI hemorrhage | 1 |
| Unknown | 3 |

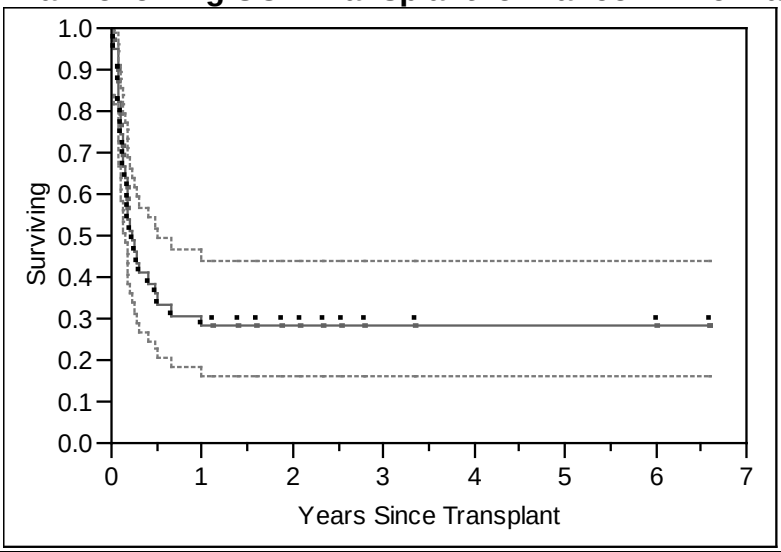
There were 8 patients who received a second transplant. All died within the first year following the initial UCB transplant.

### 6.5.4 Analysis of Primary Endpoint(s)

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown in Figure 29 below for the 39 FA patients in the Docket datasets. The estimated mortality is about 64% in the first 6 months and 72% by the end of the first year, so that the probability of survival plateaus at 28% after a year. The numbers at risk at 3 years and beyond is low. Median follow-up was 0.2 years.

**Figure 29: Survival Following UCB Transplant for Fanconi Anemia – Docket Data**

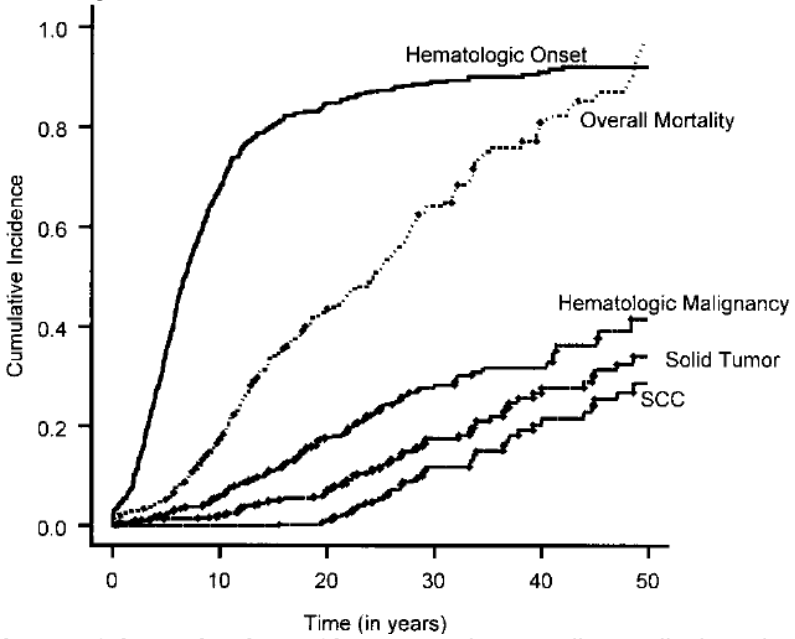



| Year | 0 | 0.5 | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|---|
| Survival | 1.00 | 0.36 | 0.28 | 0.28 | 0.28 | 0.28 | 0.28 | 0.28 |
| No. at Risk | 39 | 14 | 11 | 7 | 3 | 2 | 2 | 2 |

## Historical Experience

The International Fanconi Anemia Registry (IFAR) was established in 1982 and is the only substantial source of historical data regarding FA. In the most recent analysis of survival data from IFAR, Kutler reported on 754 FA patients followed for a median of 10.6 years (Kutler and Singh et al. 2003). A graphic showing overall mortality is reproduced in Figure 30. The mortality is approximately linear with age, rising at a rate of about 2% per year.

**Figure 30: Mortality and Other Outcomes in Fanconi Anemia Patients – IFAR**




**Cumulative incidence of the end points of interest.** The overall mortality is estimated by means of the Kaplan-Meier method. Overall survival rate is 1 – overall mortality rate. The cumulative incidence of all the other end points are calculated by treating death as a competing cause of risk. [SCC = squamous cell carcinoma, Hematologic Onset = plt < $100x10^9$/L, Hgb < 10 g/dL, or ANC < $1x10^9$/L]
Source: Kutler and Singh et al. 2003

The article provided a display of only overall mortality, regardless of bone marrow status or transplant history, but the results of some additional analyses were reported. A subset of 593 patients experienced bone marrow failure (BMF), which was defined in that study as plt < 100 x $10^9$/L, Hgb < 10 g/dL, or absolute neutrophil count (ANC) < 1 x $10^9$/L. Of this group, 219 received HSCT. However, 4 who had no follow-up after receiving HSCT were not included, leaving 215 HSCT patients with follow-up. Using a Cox regression of the time-dependant covariate for HSCT, the hazard ratio for HSCT was estimated to be 5.0 (95% CI 3.8 – 6.6) in a multivariate model incorporating sex and complementation group (Table 17).

**Table 17: Overall Survival Time in the Subgroup of FA Patients with BMF, multivariate results (Cox proportional hazards model)**

| Variable | No. patients | Hazard ratio (95% CI) | P |
|---|---|---|---|
| Group | | | |
| A/G | 212 | 1.0† | NA |
| C | 72 | 1.7 (1.2-2.6) | .007 |
| Nontyped* | 305 | 1.5 (1.2-2.1) | .004 |
| Sex | | | |
| Female | 290 | 1.0† | NA |
| Male | 299 | 1.3 (1.0-1.7) | .06 |
| HSCT | 589 | 5.0 (3.8-6.6) | < .0001 |

N/A indicates not applicable
* Complementation group unknown
† Baseline
Source: Kutler and Singh et al. 2003

*Reviewer's Comments:*
*While the IFAR results of Kutler and Singh seem to indicate a greatly increased risk associated with HSCT, their criteria of BMF are less stringent that those used by other authors to define severe aplastic anemia. Since the fraction of patients receiving HSCT was only 37% of the total defined as having BMF, it is quite possible that that the results of the survival analysis reflect the possibility that going on to receive HSCT is a marker for disease progression or worsening prognosis. Even if a therapy has a moderate benefit, its selective administration to the sickest patients could give rise to a paradoxical result of apparent harm in an epidemiologic study such as this. Further, early experience in HSCT for FA showed that these patients do poorly unless they have a reduced-intensity conditioning regimen; some fraction of the patients in this study may not have received the currently recommended regimen. The report does not provide enough additional data to be able to evaluate these possibilities. The findings from Kutler need to be interpreted cautiously, but they do seem to run counter to the notion that the HSCT treatment could be expected to provide a dramatic sustained survival benefit in most patients.*

*On a visual basis, the 72% one-year mortality observed in the docket datasets well exceeds the mortality in FA over even a decade for the first 30 or 40 years of life as reported from the IFAR experience. However, a much more relevant comparison would be against patients in the IFAR database after they had developed a severity of bone marrow failure that would make them transplant candidates. The available data do not accommodate that analysis. The closest approximation to doing such a comparison is the hazard analysis reported by Kutler, which suggested harm rather than benefit from HSCT, but which is not specific to UCB and which is subject to the difficulties in interpretation as noted above.*

### 6.5.5 Analysis of Secondary Endpoint(s)

The potential to substantiate claims for clinical benefits other than survival was not evaluated because no other disease-specific outcome data were included in the Docket datasets.

### 6.5.7 Subpopulations

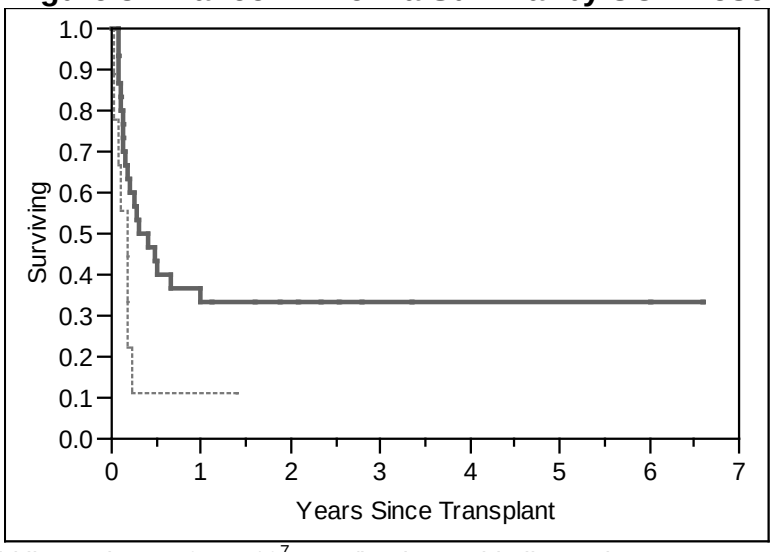
Of the 39 patients with Fanconi anemia, gender was not recorded for 30 (77%) and race was not recorded for 31 (79%).

By proportional hazards analysis, none of the variables age, gender, or race appeared to be related to survival outcome, either in univariate analyses, or with adjustment for dose. In a multivariate analysis incorporating age, gender, and race (n = 9, due to missing data), none of the variables had a significant relationship with survival outcome ($p > 0.40$ for all). (A multivariate analysis that also included dose could not be performed due to numerical instability).

### 6.5.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A proportional hazards model found a relationship between TNC dose and survival with an estimated 15% ± 6% (SE) decrease in hazard for each increase of $10^7$ TNC/kg (nominal $p = 0.013$). There were 9 patients with a dose $< 2.5 \times 10^7$ TNC/kg. An analysis comparing these 9 patients to those with TNC doses ≥ 2.5 showed decreased survival (11% at 3 months) with the lower dose (nominal log-rank $p = 0.036$), but the survival experience with the higher dose was similar to that of the overall group (Figure 31). An analysis comparing patients with TNC doses above and below the median dose of $4.5 \times 10^7$ TNC/kg showed a trend toward improved survival for doses above the median, but the difference was not statistically significant (nominal $p = 0.14$)

**Figure 31: Fanconi Anemia Survival by UCB Dose**




Upper solid line = dose ≥ 2.5 x $10^7$ TNC/kg, lower thin line = dose < 2.5 x $10^7$ TNC/kg.

## 6.5.10 Additional Efficacy Issues/Analyses

### Published Reviews and Opinions

In a review of cord blood banking by an AAP Work Group (Work Group on Cord Blood Banking 1999), the summary of indications for allogeneic stem cell transplantation included "aplastic anemia and other cytopenias (not environmentally caused)" in the category of "effective." Those conclusions were reflected in the 2005 IOM report on cord blood (Meyer and Hanna et al., 2005). The AAP review did not provide references to specific data in support of that determination. The IOM report cited the primary sources for evidence in Fanconi anemia as several small case series and bone marrow transplant experience: Gluckman and Devergie et al. 1990, Kohli-Kumar and Shahidi et al. 1993, Aker and Varadi et al. 1999, Guardiola and Kurre et al. 2003, and Guardiola and Socie et al. 2004. More recent reviews addressing the use of cord blood in Fanconi anemia are found in Smith and Wagner 2009, which cites evidence in Gluckman and Rocha et al. 2007 and Wagner and Eapen et al. 2007 (although the latter reference specifically excludes consideration of cord blood). Review of the literature identified the following additional primary sources: Motwani and Lawson et al. 2005 and Ruggeri and Peffault de Latour et al. 2008. The Cochrane Collaboration has not conducted a review of the use of stem cell transplantation in Fanconi anemia.

### Published experience with UCB for Fanconi anemia

*Rubinstein and Carrier et al. 1998 (n=35)*
This is a report of 562 patients who received UCB for a wide variety of conditions. While presumably based on the same dataset as the 562 patients submitted to the

Docket, the Docket dataset from NYBC has only 30 patients with Fanconi anemia. The article reports a cumulative event-free survival at 1 year of about 20% for Fanconi anemia but does not report the overall survival for that disease.

*Motwani and Lawson et al. 2005 (U-UCB n=4)*
This is a report of 7 children in the UK who received stem cell transplantation for FA. This included 4 patients, ages 5 to 10 years, who received fully matched, unrelated UCB. In one patient, the UCB was a second transplant after failure of initial BMT. All four who received UCB had engraftment with full donor chimerism. All were alive at least through 13 months, although one developed Evans syndrome and another developed an autoimmune hemolytic anemia.

*Gluckman and Rocha et al. 2007 (U-UCB n=93)*
This is a retrospective analysis of unrelated UCB transplantation in 93 patients with Fanconi anemia reported to the Eurocord Registry from 26 countries using a standardized questionnaire. Median age was 8.6 years. At the time of transplant, 87% had aplastic anemia, 9% had myelodysplastic syndrome, and 4% had acute leukemia. The HLA match was full in 13%, 1 mismatch in 38%, and 2 or 3 mismatches in 48%. Reduced-intensity conditioning regimens incorporating fludarabine were used for 61% of patients. Median follow-up was 22 months with a minimum of 3 months; only two patients were lost to follow-up. Overall survival at 1 year and beyond was 40% ± 5% (SE). In a multivariate analysis, the factors that were found to be favorably related to survival were negative CMV serology in the recipient, use of fludarabine in the conditioning regimen, and infused TNC ≥ $4.9 \times 10^7$/kg.

*Ruggeri and Peffault de Latour et al. 2008 (U-UCB n=8)*
Reports on 14 patients who received double cord transplants for bone marrow failure syndromes, including 8 with FA (of whom 2 had secondary acute leukemia). Age range was 7 to 24 years. Within 5 months, 5 of the 8 had died, including one with acute leukemia. The remaining 3 have been followed 10 to 19 months and have full donor chimerism.

Several other reports of UCB use for FA were identified in the literature but are not reviewed here in detail because the series was too small or the UCB was not unrelated: Gluckman and Broxmeyer et al. 1989 (n=1, sibling R-UCB); Gluckman and Devergie et al. 1990 (N=3, sibling R-UCB); Kohli-Kumar and Shahidi et al. 1993 (n=1, sibling R-UCB); Aker and Varadi et al. 1999 (n=1, sibling R-UCB); de Medeiros and Silva et al. 2001 (n=1); Yoshimasu and Tanaka et al. 2001 (n=1); Grewal and Kahn et al. 2004 (n=1, matched sibling R-UCB); Bielorai and Hughes et al. 2004 (n=1, matched sibling R-UCB);

*Reviewer's Comment: Published literature in Fanconi anemia generally confirms a similarly high mortality following UCB transplant.*

## 6.6 Bone Marrow Failure – (Acquired) Severe Aplastic Anemia (SAA)

For purposes of this section, severe aplastic anemia (SAA) is taken to connote diseases other than primary anemias. One definition of SAA was given by Camitta (Camitta and Thomas et al. 1976) and appears to be widely (but not universally) adopted:

> To qualify as severely aplastic, patients had to have at least two of the following three peripheral blood values: (1) granulocytes <500/cu mm (2) platelets <20,000/cu mm and (3) reticulocytes < 1% (corrected for hematocrit). In addition the marrow had to be either markedly hypoplastic (<25% of normal cellularity) or moderately hypoplastic (25%-50% of normal cellularity with < 30% of remaining cells being hematopoietic) as estimated from biopsies.

Other proposed definitions are closely similar but differ in using criteria for absolute reticulocyte count (Camitta and Thomas et al. 1979; Myers and Davies 2009) or in the marrow cellularity criteria (Howard and Naidu et al. 2004). SAA is a serious condition with a poor prognosis. Bleeding or infections can be the life-threatening complications, depending on the particular cytopenias. Prognosis may depend on the severity of the disease. Overviews of SAA often cite a general mortality of 20% by 1 year.

Atgam (lymphocyte immune globulin) is an immunosuppressive therapy (IST) approved in 1981 as treatment for patients with SAA who are unsuitable for bone marrow transplantation. Other immunosuppressive therapies (antithymocyte globulin and cyclosporine), while not FDA-approved for that purpose, are also used to treat SAA.

### 6.6.1 Methods

Efficacy was evaluated by computing estimates for post-transplant survival obtained from pooling the three datasets described in Section 5.1. Results were compared to historical control survival data obtained from the literature. The literature was reviewed for additional reports of experience with unrelated cord blood use in SAA.

In the Docket datasets, diagnostic information other than the diagnosis of SAA was not provided. Thus, eligibility and diagnostic criteria for the series are unknown. There was no explicit representation of a patient's hematologic status at the time of UCB transplantation. Information on disease-specific outcomes that might have been of interest, such as blood counts, bone marrow analysis, infections, or bleeding events was not provided.

### 6.6.2 Demographics

Basic demographics for all the severe aplastic anemia (SAA) patients in pooled datasets are shown in Table 18 below, together with basic treatment data. Demographic information other than age was not provided in the NYBC dataset.

**Table 18: Demographics and Treatment Data for Patients with SAA – Docket Data**

| | |
|---|---|
| Total N | 37 |
| Age in Years | |
| Mean (SD) | 12 (11) |
| Median (Range) | 7 (0 – 44) |
| Gender | |
| Male | 27% (10) |
| Female | 19% (7) |
| Unknown | 54% (20) |
| Race | |
| Caucasian | 32% (12) |
| African/African-American | 8% (3) |
| Asian | 5% (2) |
| Unknown | 54% (20) |
| Dosing (TNCx$10^7$/kg prefreeze) | |
| Median | 3.8 |
| $10^{th}$, $25^{th}$, & $75^{th}$ percentiles | 1.8, 2.8, 5.5 |
| Dose < 2.5 | 22% (8) |
| HLA Match | |
| 6/6 | 3% (1) |
| 5/6 | 43% (16) |
| 4/5 | 43% (16) |
| 3/6 | 5% (2) |
| 2/6 | 3% (1) |
| Unknown | 3% (1) |
| Data source | |
| NMDP | 46% (17) |
| NYBC | 54% (20) |

**Figure 32: Age Distribution of Severe Aplastic Anemia Patients – Docket Data**

### 6.6.3 Subject Disposition

Of the 37 total patients with severe aplastic anemia, 24 are reported to have died. The causes of death were:

**Table 19: Causes of Death in Severe Aplastic Anemia Patients**

| | N |
|---|---|
| Infection/Sepsis | 8 |
| Respiratory | 5 |
| Hemorrhage | 3 |
| GVHD | 2 |
| Multi-organ failure | 2 |
| Misc.* | 4 |

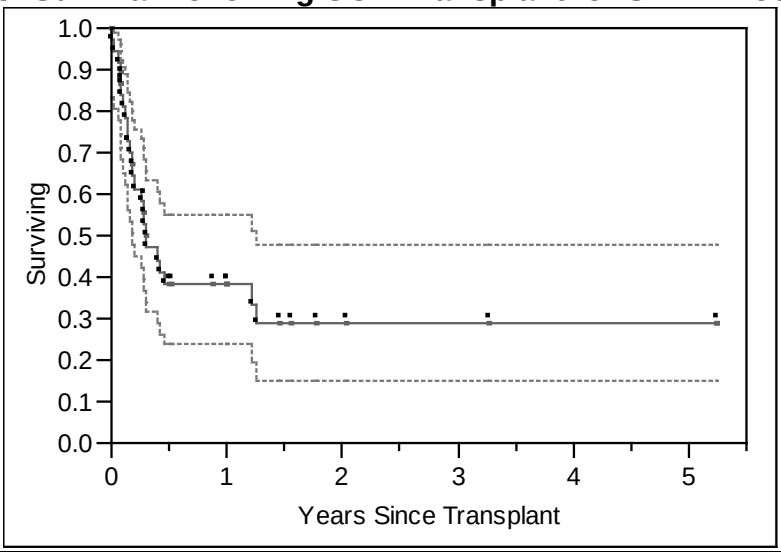
* Graft failure-1, "RECUR/RESDL LEUK"-1, other, unspecified-1, unknown-1.

### 6.6.4 Analysis of Primary Endpoint(s)

Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown in Figure 33 below for the 37 patients with SAA from the pooled docket datasets. The mortality is about 62% in the first 6 months. The probability of survival plateaus at 29% after 15 months, with the lower end of the confidence interval at 16%. Median follow-up was 0.3 years.

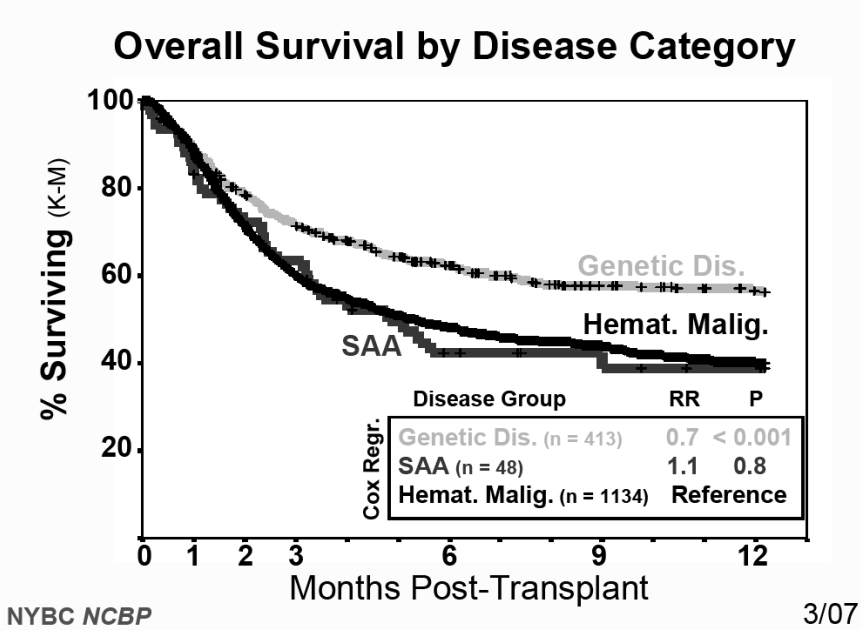
**Figure 33: Survival Following UCB Transplant for SAA – Docket Data**




| Year | 0 | 0.5 | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|---|
| Survival | 1.00 | 0.38 | 0.38 | 0.29 | 0.29 | 0.29 | 0.29 | 0.29 |
| No. at Risk | 37 | 13 | 8 | 3 | 2 | 1 | 1 | 1 |

A summary analysis of SAA that was submitted as one of the Docket documents is shown in Figure 34. The population used for the analysis presumably overlaps with patients represented in the dataset submitted to the Docket by NYBC (listed as item 2 under Section 5.1, above), but the NYBC dataset had only 20 cases with a diagnosis coded as "SAA," whereas the summary analysis included 48. The results of the summary analysis show slightly less than 40% survival after 1 year, which is higher than the 29% survival probability estimated from the analysis of the Docket pooled datasets shown in Figure 33.

**Figure 34: Survival following SAA (& Other Conditions) following UCB – Summary Results Reported by NYBC**




Source: (Docket document FDA-2006-D-0157-DRAFT-0064, -0065)

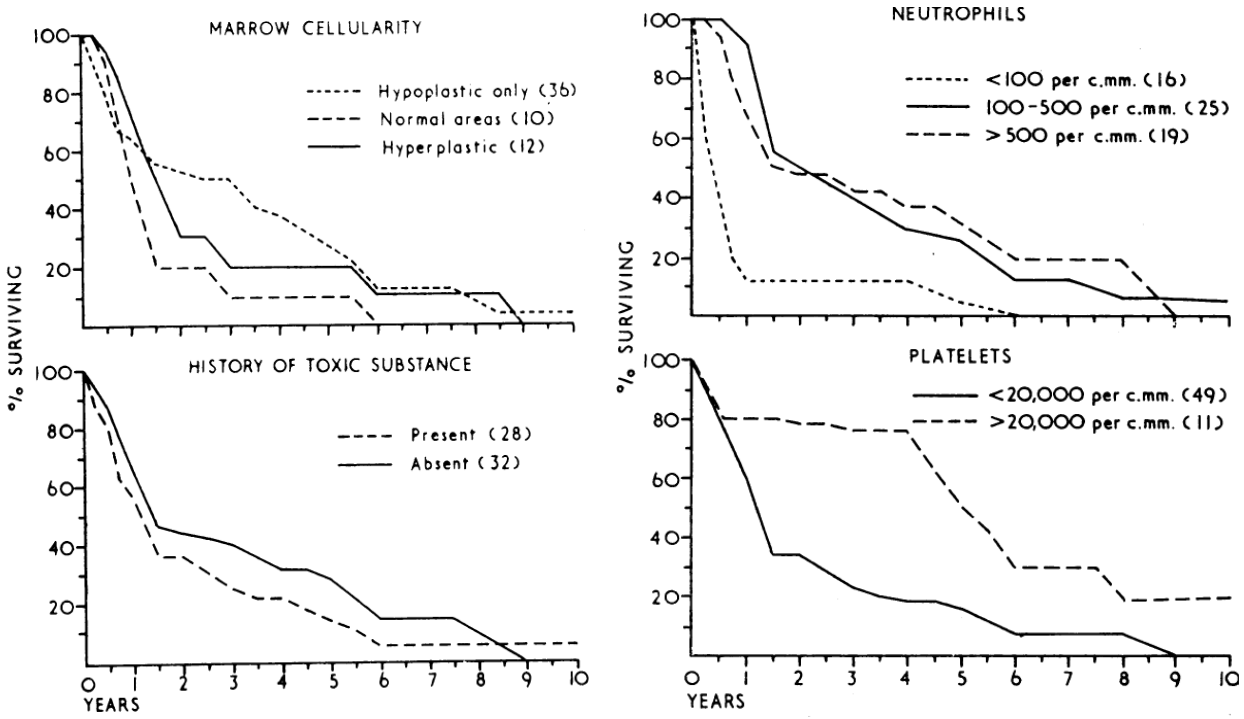
## Historical Experience

In contrast to the conditions considered previously, there is a relative abundance of potential sources of historical survival data in SAA. There is, as well, variability in the reported survival experience. The earlier reports come close to providing data that can be regarded as reflecting natural history. Reports of large series published in the past decade have consisted of patients who have received immunosuppressive therapy (IST). While less like natural history, these historical data may still be relevant either for providing a germane control group in IST failures or for consideration in a risk/benefit assessment.

A series of 60 patients with acquired aplastic anemia was reported by Lewis in 1965 along with an analysis to identify prognostic factors. The exact diagnostic criteria were

not described. Given the date of the series, none is presumed to have received HSCT. A majority received steroid or anabolic hormones and intermittent transfusions.

**Figure 35: Survival in 60 Patients with Acquired Aplastic Anemia – Lewis 1965**

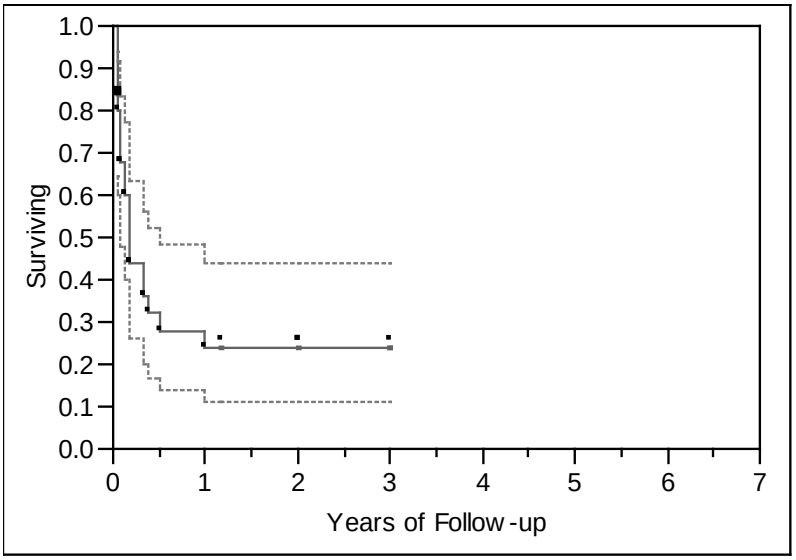



Source: Lewis 1965

The report illustrated how prognosis can vary depending on cell counts. Overall survival appeared to be 55% to 65% at 1 year and 35% to 45% at 2 years.

In 1972 Davis reported on a series of 25 patients with acquired aplastic anemia (Davis and Rubin 1972). Data were tabulated, but survival analysis was not presented. The report states that "Six patients received allogeneic bone marrow infusions without sustained benefit." Transcribing from the tabulated data, this Reviewer was able to present the outcomes for the 19 untransplanted patients as a survival analysis, which is presented in Figure 36. The survival at 1 year is estimated to be approximately 24%.

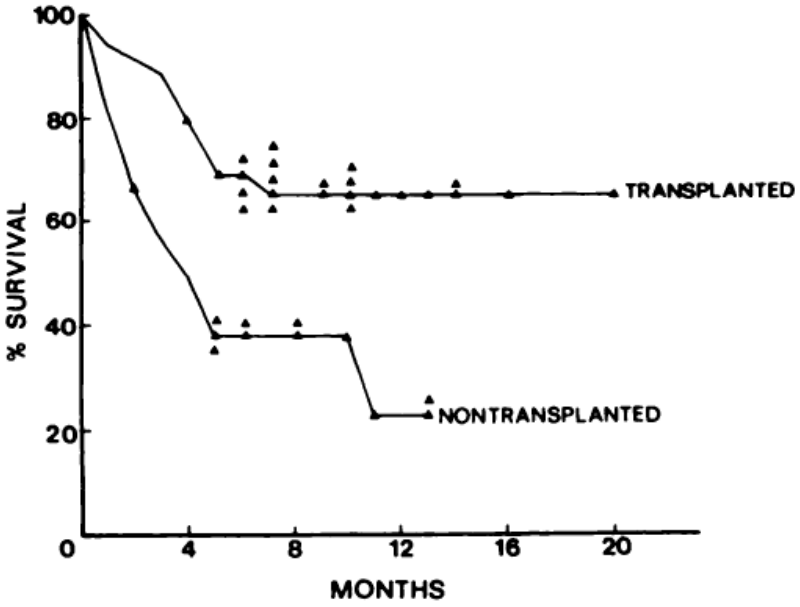
**Figure 36: Survival of 19 Untransplanted Patients with Aplastic Anemia – Davis 1972**




Source: Reviewer's graph of published tabulated data in Davis and Rubin 1972

Camitta presented a prospective study of 67 patients with SAA randomized to BMT according to the availability of a matched sibling (Camitta and Thomas et al. 1976). In the study, there were 31 patients who were not transplanted. The 1-year survival in the latter group was just over 20%, and survival was statistically significantly better in the transplanted group.

**Figure 37: Life Table Plot of the Effect of Sibling BMT on Survival in SAA – Camitta 1976**

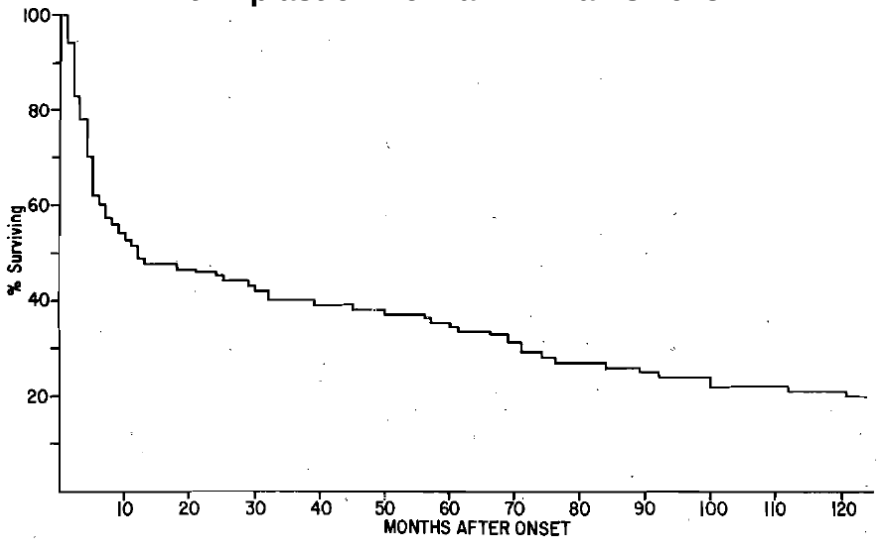



Life table plot of the effect of treatment on survival in severe aplastic anemia. Triangles indicate duration of follow-up of current survivors.

Source: Camitta and Thomas et al. 1976

In a study of 101 patients with aplastic anemia seen in Utah between 1944 and 1972 (Williams and Lynch et al. 1978) the 1-year survival was about 50%. The use of HSCT was not described.

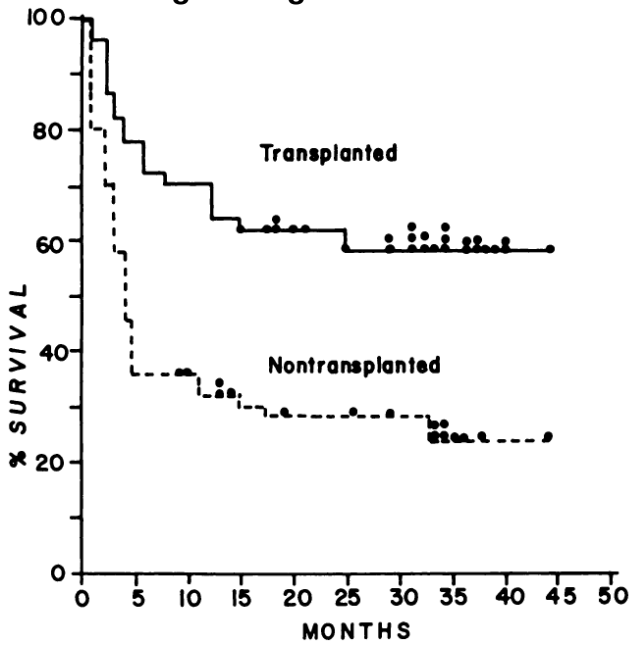
**Figure 38: Survival after the Onset of Symptoms in 101 Patients with Aplastic Anemia – Williams 1978**




Source: Williams and Lynch et al. 1978

In what appears to be an extension of the study reported in 1976, Camitta reported on a larger series of patients prospectively “randomized” to BMT based on availability of a matched sibling (Camitta and Thomas et al. 1979). The analysis appears to show a substantial improvement in survival for the 43 transplanted patients compared to 63 untransplanted patients. In that series, the untransplanted 1-year survival appeared to be slightly greater than 30% (Figure 39), which was within the range of the previous historical results.

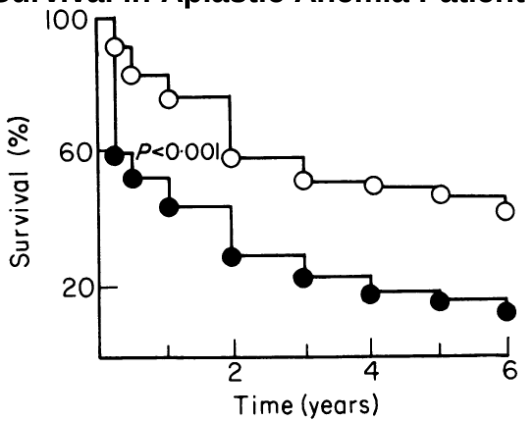
**Figure 39: Survival Following Sibling BMT or No BMT in SAA – Camitta 1979**




Source: Camitta and Thomas et al. 1979

A series of patients in England with SAA, excluding FA, was reported by Mir; none was treated with HSCT (Mir and Geary 1980). Exact diagnostic criteria were not stated. In the subset of 55 patients with the more severe disease, as judged by cell counts and speed of onset, the 1-year survival was close to 50%.

**Figure 40: Survival in Aplastic Anemia Patients – Mir 1980**




Patients were allocated in the 2 groups on the basis of the speed of onset of illness and the initial hemoglobin and platelet values. Patients in the smaller group of 55 [filled circles] had a rapid onset, lower hemoglobin and platelet values at diagnosis and an acute course.
Source: Mir and Geary 1980

In 1989 Halperin (Halperin and Grisaru et al. 1989) reported on a series of 34 children with acquired SAA (diagnosed by standard criteria) treated at Toronto, of whom 20 did not receive HSCT but had either immunosuppression or supportive care (consisting of transfusions and antimicrobial agents; these were patients diagnosed prior to availability of antithymocyte globulin). The 8 who had only supportive care had estimated survival through 2 years of about 25%.

**Figure 41: Survival in Children with SAA – Halperin 1989**

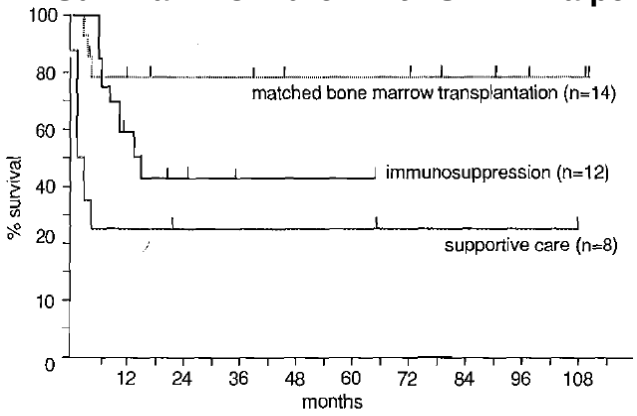


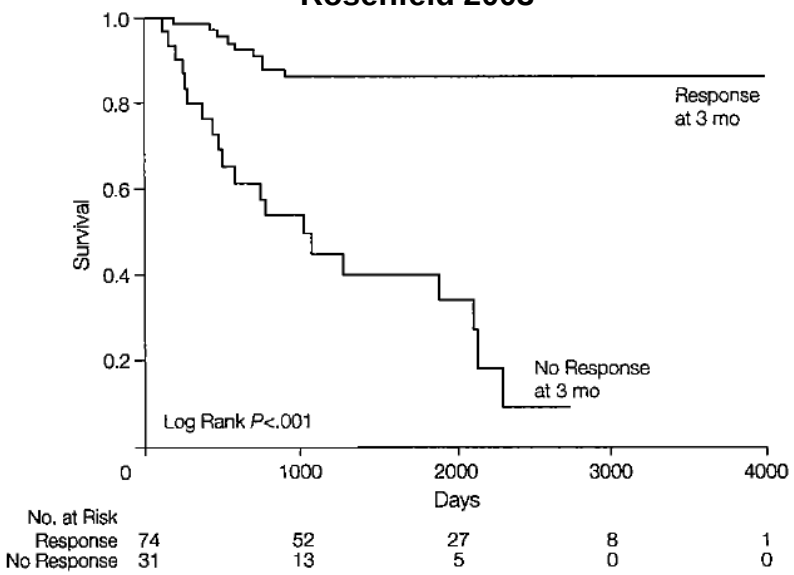

**FIG. 1.** Survival curves for children with severe acquired aplastic anemia treated with allogeneic histocompatible bone marrow transplantation, immunosuppression with antithymocyte globulin and/or high-dose corticosteroids, or supportive care. Ticks indicate latest follow-up examination of each patient.

The available natural history data for aplastic anemia were reviewed by Heimpel (Heimpel 2000), who reported median survival ranging from 10 months, in a series of

101 cases seen from 1944 to 1973 (Williams and Lynch et al. 1978), to 20 months in his series of 70 patients through 1974. In the subset of his patients meeting criteria for severe, median survival was only 10 months. His review of more recent series found median survival of 20 to 60 months. A significant fraction of remissions in acquired SAA were reported when patients were treated with antithymocyte globulin (Sanchez-Medal and Gomez-Leal et al. 1969).

Rosenfeld and Follmann et al. 2003 reported on 122 patients who received immunosuppressive therapy (IST) in the form of antithymocyte globulin and cyclosporine in a study at NIH. At 1 year, 58% responded, and the 7-year overall survival was 55%. In the subgroup that did not respond to IST by 3 months, the 5-year survival was 40%, compared to 86% in the IST responders (Figure 42).

**Figure 42: Survival in SAA in Patients Not Responding to Antithymocyte Globulin – Rosenfeld 2003**




Overall survival of 122 patients with severe aplastic anemia treated with antithymocyte globulin and cyclosporine; median follow-up was 7.2 years. Recovery defined by blood count no longer satisfying severity criteria.
[There was 13% mortality prior to the 3-month evaluation. Four non-responders have matched, unrelated BMT; all died. Three responders had matched, related BMT; one survived.]
Source: Rosenfeld and Follmann et al. 2003

In 2009 Scheinberg (Scheinberg and Wu et al. 2009) reported the results of a prospective, randomized trial of standard immunosuppressive regimen (antithymocyte globulin plus cyclosporine) with or without the addition of sirolimus for 77 patients older than 2 years meeting the criteria for SAA (using marrow cellularity < 30%). The study excluded those with Fanconi anemia, prior immunosuppressive therapy, HIV seropositivity, underlying clonal disorder, or other significant comorbidity. The 3-year survival was 90% or better in each group (Figure 43).

**Figure 43: Survival in Immunosuppressive Trial for SAA – Scheinberg 2009**

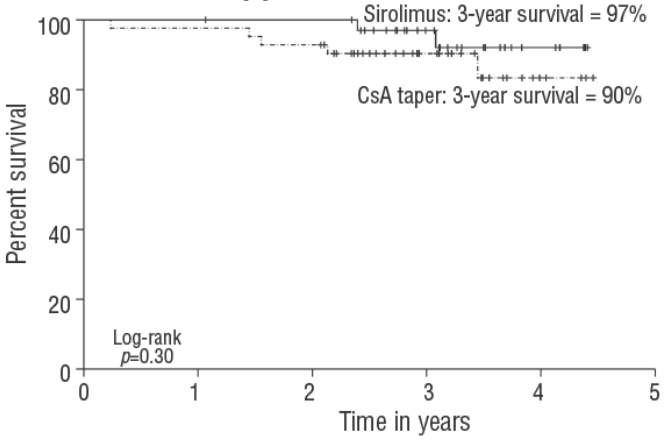
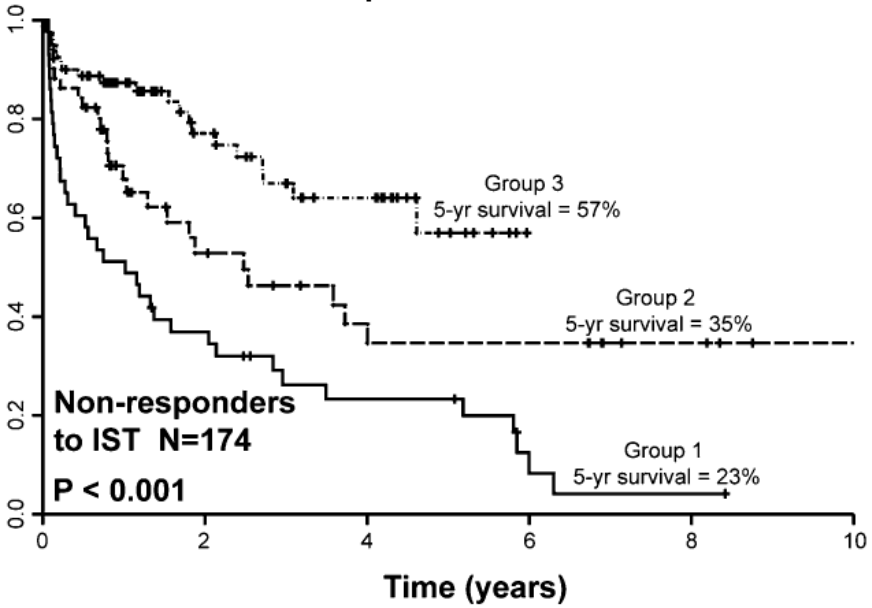



Figure 3. Overall survival for patients in the h-ATG/CsA/sirolimus (solid line) and h-ATG/CsA taper arm (dotted line). Patients who underwent hematopoietic stem cell transplantation were censored at the time of transplantation.

Source: Scheinberg and Wu et al. 2009

Most recently, Valdez (Valdez and Scheinberg et al. 2011) reported on changes over the preceding 20 years in survival for patients who were not responsive to immunosuppressive therapy, and presented survival curves censored by HSCT (Figure 44). In the most recent cohort (Group 3, 2002 – 2008), the 5-year survival was 57%.

**Figure 44: Survival in IST Non-Responders in Past Two Decades – Valdez 2011**




Survival probability for patients not responding to immunosuppressive therapy. Group 1 = 1989–1996, Group 2 = 1996–2002, Group 3 = 2002–2008. Survival is censored at time of hematopoietic stem cell transplant.
Source: Valdez and Scheinberg et al. 2011

*Reviewer's Comments:*
*The experience with severe aplastic anemia in the datasets provided in the Docket do not demonstrate post-transplant survival that improves meaningfully upon the experience of untransplanted patients as found in the literature.*

*The survival experience for SAA in the docket datasets (38% survival at 1 year, 29% at 2 years) or from the summary data submitted to the docket (40% at 1 year) appears to fall in the lower part of the range of outcomes seen in the earlier historical data. Although the analysis reported by Camitta (Figure 39) suggest effectiveness of BMT in improving survival, the docket experience for UCB more closely resembled the No BMT group from that report. The docket survival experience also appears inferior to that reported for SAA patients who have not responded to IST.*

### 6.6.5 Analysis of Secondary Endpoint(s)

The potential to substantiate claims for clinical benefits other than survival was not evaluated because no other disease-specific outcome data were included in the Docket datasets.

### 6.6.7 Subpopulations

Of the 37 patients with SAA, gender and race data were not recorded for 20 (54%).

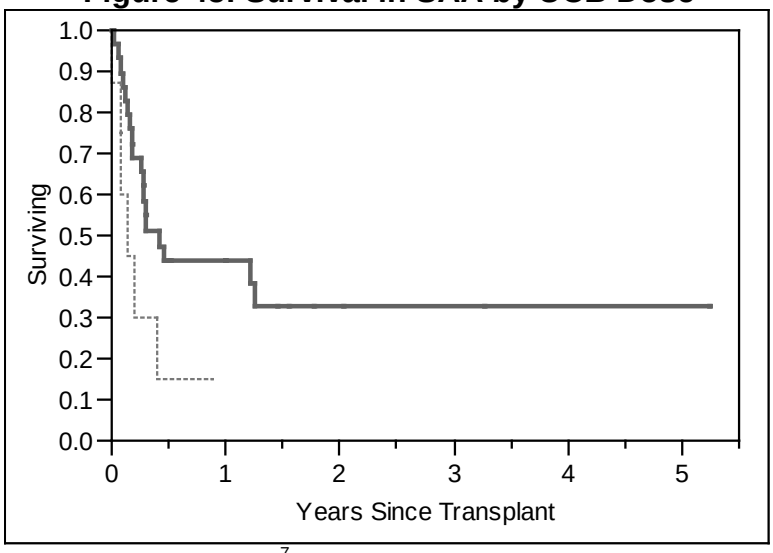
By proportional hazards analysis, neither gender nor race appeared to be related to survival outcome, either in univariate analysis or when adjusted for dose. In a univariate analysis, age appeared to increase the hazard by 3.5% ± 1.6% (SE) per year of age (nominal p = 0.044), but the relationship diminished substantially when adjusted for dose (hazard coefficient of 2.1% per year of age, p = 0.30). (See also discussion in Section 6.6.8 below.)

In a multivariate analysis (n = 17) incorporating age, gender, race, and dose, none of the variables was statistically significantly related to survival outcome (p = 0.78 for age, p = 0.21 for gender, p = 0.91 for race, and p = 0.15 for dose in the multivariate analysis).

### 6.6.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A proportional hazards model using the docket datasets found a significant relationship between TNC dose and survival, with an estimated 15% ± 8% (SE) decrease in hazard for each increase of $10^7$ cells/kg (nominal p = 0.021). There were 8 patients with a dose < 2.5 x $10^7$ TNC/kg. An analysis comparing these 8 patients to those with TNC doses ≥ 2.5 x $10^7$ TNC/kg showed a trend toward decreased survival (15% at 5 months) with the lower dose (nominal log-rank p = 0.0620), but the survival experience with the higher dose was similar to that of the overall group (Figure 45). An analysis comparing patients with TNC doses above and below the median dose of 3.8 x $10^7$ TNC/kg found no statistically significant difference and showed similar survival curves for both groups through the first year (after which numbers at risk were too small for meaningful comparison).

**Figure 45: Survival in SAA by UCB Dose**




Upper solid line = dose ≥ 2.5 x $10^7$ TNC/kg, lower thin line = dose < 2.5 x $10^7$ TNC/kg.

Age and dose were inversely related. In a proportional hazards model incorporating both age and dose, there was a relationship to survival outcomes overall (nominal p = 0.40), but neither variable was significantly related to survival outcome after adjustment for the other (p = 0.12 for dose, p = 0.30 for age). In that model, the estimated effect of dose was a reduction in hazard of 11% ± 8% (SE) per $10^7$ TNC/kg. Although the relationship to survival outcomes is statistically slightly stronger for dose than for age, observational data such as these cannot identify the causative factor(s), if any, underlying the apparent relationships.

### 6.6.10 Additional Efficacy Issues/Analyses

#### Published Reviews and Opinions

In a review of cord blood banking by an AAP Work Group (Work Group on Cord Blood Banking 1999), the summary of indications for allogeneic stem cell transplantation included "aplastic anemia and other cytopenias (not environmentally caused)" in the category of "effective," and those conclusions were reflected in the 2005 IOM report on cord blood (Meyer and Hanna et al., 2005). The AAP review did not provide references to specific data in support of that determination. However, this category of diseases appears to exclude acquired aplastic anemia, and SAA is not otherwise addressed. The Cochrane Collaboration has not reviewed the use of stem cell transplantation in aplastic anemia; however, a report on that topic is in the protocol stage.

#### Published experience with UCB in SAA

Search of the literature identified the following additional experience with UCB in SAA:

*Rubinstein and Carrier et al. 1998 (n=21)*
This is a report of 562 patients who received UCB for a wide variety of conditions. While presumably based on the same dataset as the 562 patients submitted to the Docket, the Docket dataset from NYBC analyzed above has only 20 patients with Fanconi anemia. The article reports a cumulative event-free survival at 1 year of about 20% after UCB transplant for SAA but does not report overall survival.

*Mao and Wang et al. 2004 (n=6)*
This appears to be a report of the first six patients subsequently reported in Mao and Zhu et al. 2005, described below.

*Mao and Zhu et al. 2005 (n=9)*
This is a report of 9 adults in China transplanted with UCB for SAA. Average age was 25 years. All had failed one course of immunosuppressive therapy. Conditioning regimen used cyclophosphamide and antithymocyte globulin. Dose ranged from 1.9 to 4.4 x $10^7$ per unit MNC/kg post-thaw [MNC not defined]; 6 patients received two units.

In patients who received two units, only one of the two engrafted. At a median follow-up of 32 months, 7 patients (78%) were alive.

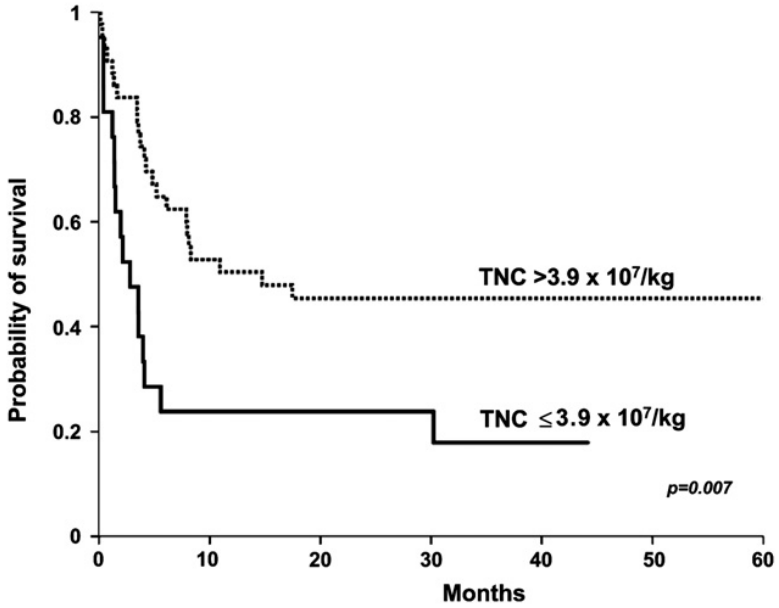
*Chan and McDonald et al. 2008 (n=9)*
This is a report of 9 children treated with UCB for SAA in Texas. Median age was 9 years. All had failed at least on course of immunosuppressive therapy. Three did not engraft with the first transplant, but two of those were engrafted after a second transplant. With a median follow-up of 34 months, 7 patients (78%) remained alive.

*Yoshimi and Kojima et al. 2008 (n=31)*
This is a report of 31 patients in Japan with SAA who received UCB as their initial stem cell transplant. Median age was 27 years (range 0.9 – 72). There were 25 who had previous immunosuppressive therapy. A variety of conditioning regimens were used. At a median follow-up of 34 months, 13 were alive, with an estimated 2-year overall survival of 41% (95% CI: 24% – 58%).

*Jaing and Huang et al. 2011 (n=5)*
This was a retrospective review of 5 children aged 3.8 to 16 treated with unrelated UCB for relapsed or refractory SAA after failing one or more courses of IST. Median time since diagnosis was 16 months. Conditioning used fludarabine, cyclophosphamide, and antithymocyte globulin. The TNC dose was at least $3.7 \times 10^7$ for four patients. All patients were alive and transfusion independent at a median follow-up of 25 months (range 7 to 34), but one subsequently received sibling UCB transplant and one had autologous recovery.

*Peffault de Latour and Purtill et al. 2011 (n=71)*
This is a retrospective analysis of 71 patients with SAA reported to Eurocord from 32 centers. The age range was 2 to 68 years with a median of 13 years; 61% were under 18. Of the 71, 13% had a diagnosis of paroxysmal nocturnal hematuria. Conditioning regimen was reduced intensity in 68%, with 46% being fludarabine-based. Double cord transplantation was given to 19%. For the single-cord transplants, HLA match was 6/6 for 10%, 5/6 for 33%, 4/6 for 51%, and 3/6 for 6%. Median follow-up was 35 months with a minimum of 8 months. The 3-year overall survival was 38% ± 6% (SE). In a multivariate analysis, only prefreeze TNC dose > $3.9 \times 10^7$/kg was associated with improved survival (Figure 46). (The dose cut point was selected after analysis of the data.)

**Figure 46: Survival in SAA Following UCB Transplantation from Eurocord Registry – Peffault de Latour 2011**




Estimated 3-year OS according to TNC dose

Source: Peffault de Latour and Purtill et al. 2011

The discussion in the article notes:

> The results of well-designed prospective trials, like one currently underway in France, which incorporate the requirement of a large cell dose and hopefully demonstrate better OS [overall survival], are needed before including UCBT [unrelated cord blood transplantation] in the treatment strategy for SAA can be recommended." (Peffault de Latour and Purtill et al. 2011)

*Yamamoto and Kato et al. 2011 (n=12)*

This is a report of 12 consecutive adult patients in Japan treated with UCB for SAA, of which 6 were very severe and 2 were fulminant. All but the fulminant cases had failed to respond to immunosuppressive therapy. All patients received a reduced-intensity conditioning regimen. Two of the very severe cases died; the remaining patients are alive at a median of 36 months. The estimated 3-year overall survival is 83%.

Several other reports of UCB use for SAA were identified in the literature but are not reviewed here in detail because the series was too small or the UCB was not unrelated: Shaw and Haut et al. 1999 (n=3); Fruchtman and Hurlet et al. 2004 (n=1, autologous UCB); Ohga and Ichino et al. 2006 (n=1); Tajika and Mizuki et al. 2007 (n=2); Kosaka and Yagasaki et al. 2008 (n=2 among a much larger group receiving BMT); Stepensky and Revel-Vilk et al. 2008 (n=1, related UCB + BMT); Lee and Kang et al. 2009 (n=1); Kang and Lee et al. 2010 (n=1).

## 6.7 Beta Thalassemia

Beta thalassemia is a congenital disorder of hemoglobin production due to a mutation affecting beta-globin synthesis. In the severe form, beta thalassemia major, patients present with severe anemia in the first year of life. They are dependent on regular blood transfusions for survival, typically 1 to 3 units every 3 to 5 weeks. Iron overload is a complication of treatment. Although approved chelation therapy is available, compliance is difficult, and heart, liver, and endocrine damage from iron overload are common complications. Patients often die in the middle decades.

For patients being considered for bone marrow transplantation, prognosis following transplant is associated with the Pesaro classification, which is a scoring system based on hepatomegaly, liver fibrosis, and regularity of chelation therapy (Lucarelli and Galimberti et al. 1990). Class 1 represents the best prognosis, and Class 3 is the worst.

### 6.7.1 Methods

Efficacy was evaluated by computing estimates for post-transplant survival obtained from pooling the three datasets described in Section 5.1. Results were compared to historical control survival data obtained from the literature. The literature was reviewed for additional reports of experience with unrelated cord blood use in beta thalassemia. Review of reasonably well documented case reports in the Docket was also contributory.

In the Docket datasets, diagnostic information other than the diagnosis of beta thalassemia was not provided. Thus, eligibility criteria for the series and clinical status at time of transplant are unknown. Information on disease-specific outcomes other than survival that might have been of interest, such as transfusion requirements or hemoglobin profile, were not provided in the datasets. The Docket included case reports that provided data useful for evaluating efficacy regarding endpoints other than survival.

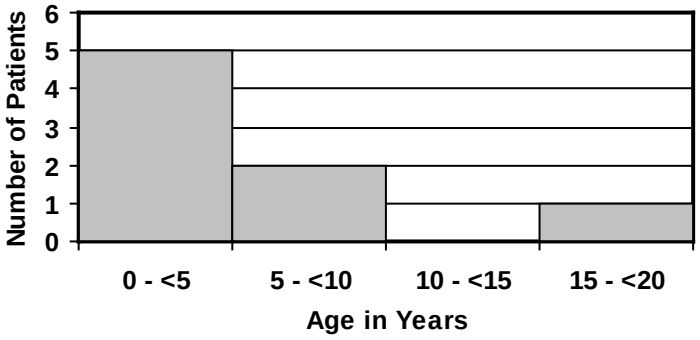
### 6.7.2 Demographics

The case series is described in a subsequent section. Basic demographics for the patients with beta thalassemia in pooled datasets are shown in Table 20 below, together with basic treatment data. Demographic information other than age was not provided in the NYBC dataset.

**Table 20: Demographics and Treatment Data for Patients with Beta Thalassemia – Docket Data**

| | |
|---|---|
| Total N | 8 |
| Gender | |
| Male | 13% (1) |
| Female | 63% (5) |
| Unknown | 25% (2) |
| Age in Years | |
| Mean (SD) | 6.2 (5.9) |
| Median (Range) | 4.2 (2.0 – 20.0) |
| Race | |
| Caucasian | 50% (4) |
| Asian | 25% (2) |
| Unknown | 25% (2) |
| Dosing (TNCx$10^7$/kg prefreeze) | |
| Median | 6.4 |
| $10^{th}$, $25^{th}$, and $75^{th}$ percentiles | 2.5, 5.1, 10.4 |
| Dose < 2.5 | 0% (0) |
| HLA Match | |
| 6/6 | 13% (1) |
| 5/6 | 75% (6) |
| 4/5 | 13% (1) |
| Data source | |
| NMDP | 75% (6) |
| NYBC | 25% (2) |

**Figure 47: Age Distribution for Patients with Beta Thalassemia – Docket Data**




(Ages were: 2.0, 2.0, 3.7, 4.2, 4.2, 5.6, 8, and 20)

## 6.7.3 Subject Disposition

No protocol was provided for this study, and there is no information available about screening, eligibility criteria, or diagnostic criteria. Of the 8 total patients with beta

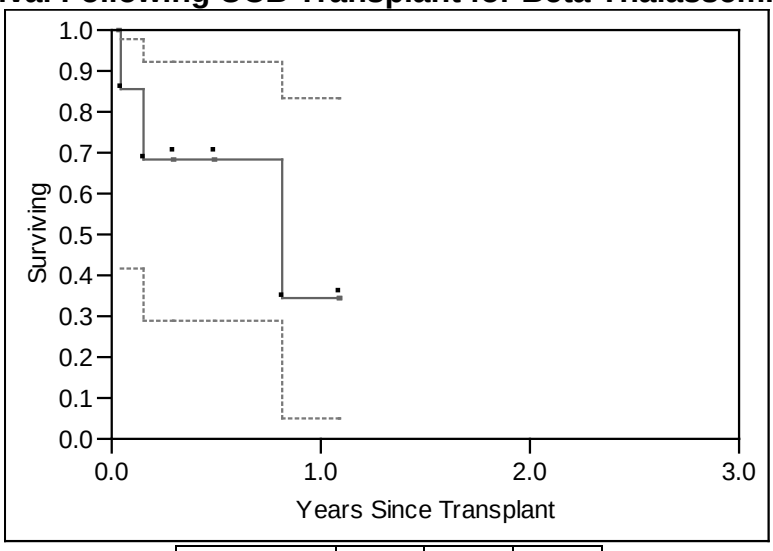
thalassemia, 3 are reported to have died: two from respiratory disease, and one from multi-organ failure.

### 6.7.4 Analysis of Primary Endpoint(s)

#### Active Treatment Experience

A Kaplan-Meier survival curve with 95% confidence intervals is shown below for the 8 patients with beta thalassemia in the Docket datasets. As estimated from the Kaplan-Meier curve, the mortality at 1 year is 66%, and the corresponding estimate of survival at 1 year is 34%. The median follow-up was 0.2 years.

**Figure 48: Survival Following UCB Transplant for Beta Thalassemia – Docket Data**

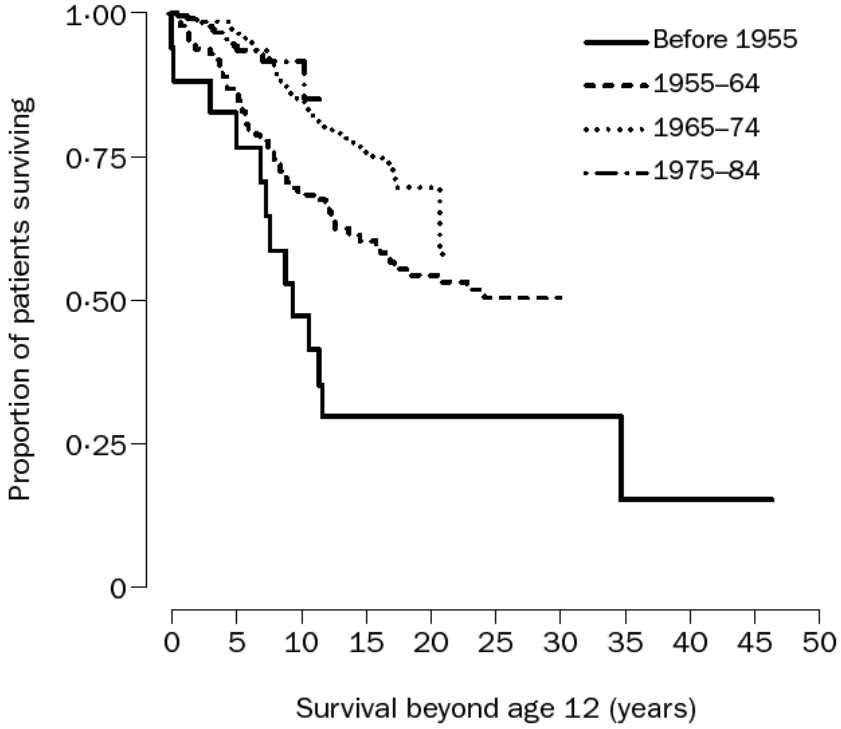



| Year | 0 | 0.5 | 1 |
|---|---|---|---|
| Survival | 1.00 | 0.69 | 0.34 |
| No. at Risk | 8 | 2 | 1 |

#### Historical Experience

In 2000, Modell evaluated the survival beyond age 12 years in patients with beta thalassemia major according to birth cohort using data from the UK Thalassemia Register (Modell and Khan et al. 2000). Modell also noted that about 50% of patients die by the age of 35 years. For the cohort born in the decade starting in 1975, it appears that around 90% of 12-year-olds survived to adulthood (Figure 49).

**Figure 49: Survival Beyond Age 12 in Beta Thalassemia by Birth Year Cohort in the UK – Modell 2000**




**Survival beyond 12 years of age by 10-year birth cohort**

Source: Modell and Khan et al. 2000

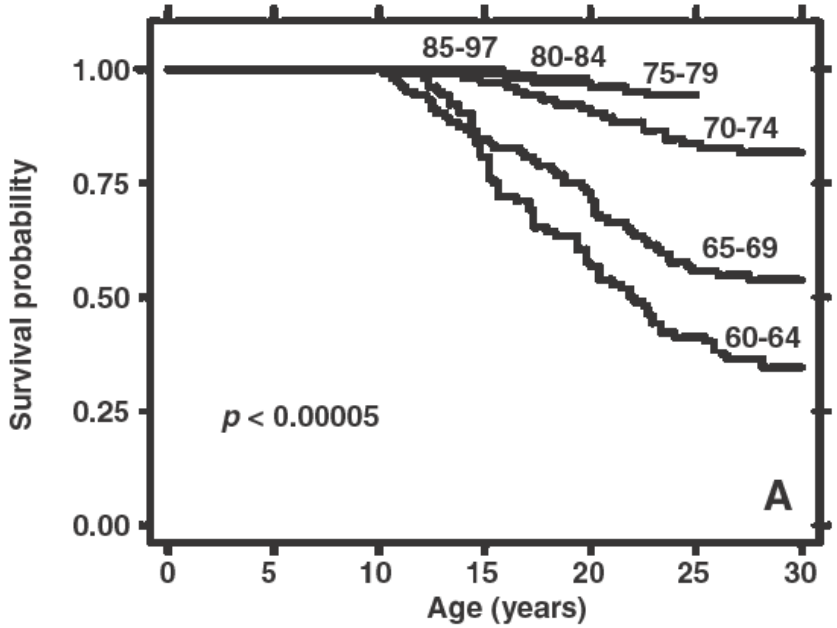
Similar analyses by Borgna-Pignatti also found a pattern of improving survival over time (Borgna-Pignatti and Rugolotto et al. 1998; Borgna-Pignatti and Rugolotto et al. 2004).

**Table 21: Survival by Birth Cohort at Different Ages of Patents with Transfusion-Dependent Thalassemia – Borgna-Pignatti 1998**

| Age (years) | 1970–1974 | 1975–1979 | 1980–1984 |
|---|---|---|---|
| 10 | 98% (96–99) | 98% (96–99) | 99% (95–100) |
| 15 | 95% (92–97) | 97% (94–98) | 98% (93–100) |
| 20 | 89% (85–92) | 96% (93–98) | |
| 25 | 82% (77–86) | | |

Source: Borgna-Pignatti and Rugolotto et al. 1998

**Figure 50: Survival in Beta Thalassemia Without Transplantation by Birth Year Cohort – Borgna-Pignatti 2004**




Source: Borgna-Pignatti and Rugolotto et al. 2004

From Figure 50, it appears that the most recent birth cohorts have a better than 95% probability of reaching age 20 years.

## HSCT Experience Not in the Docket

Lucarelli observed about a 60% multi-year survival using BMT for beta thalassemia in adults (Lucarelli and Clift et al. 1999), but much higher survival rates with BMT in adolescents (Lucarelli and Gaziev 2008).

**Figure 51: Survival following Sibling BMT in Adults with Beta Thalassemia – Lucarelli 1999**

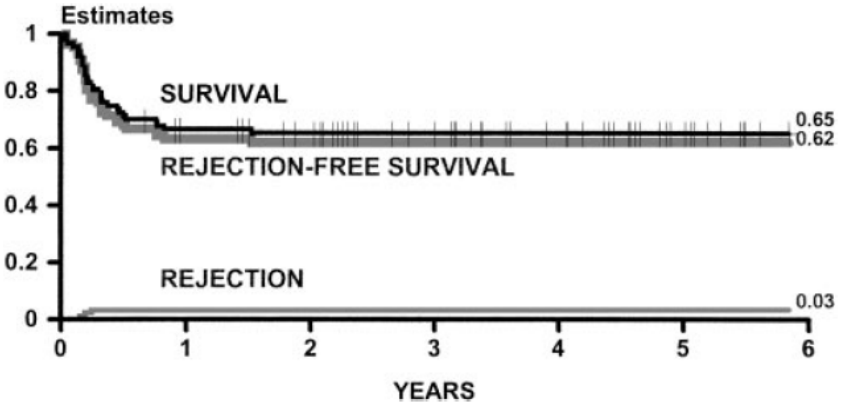



**Fig 2. Kaplan-Meier estimates of survival and rejection-free survival and cumulative incidence estimates of rejection for 87 adult patients transplanted between May 1991 and September 1996. This experience is updated as of December 1997.**

Source: Lucarelli and Clift et al. 1999

**Figure 52: Survival Following Allogeneic BMT in Beta Thalassemia in Adolescents – Lucarelli 2008**

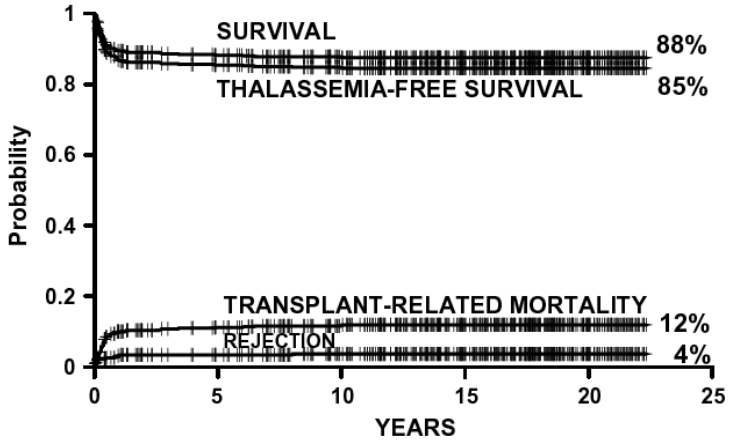


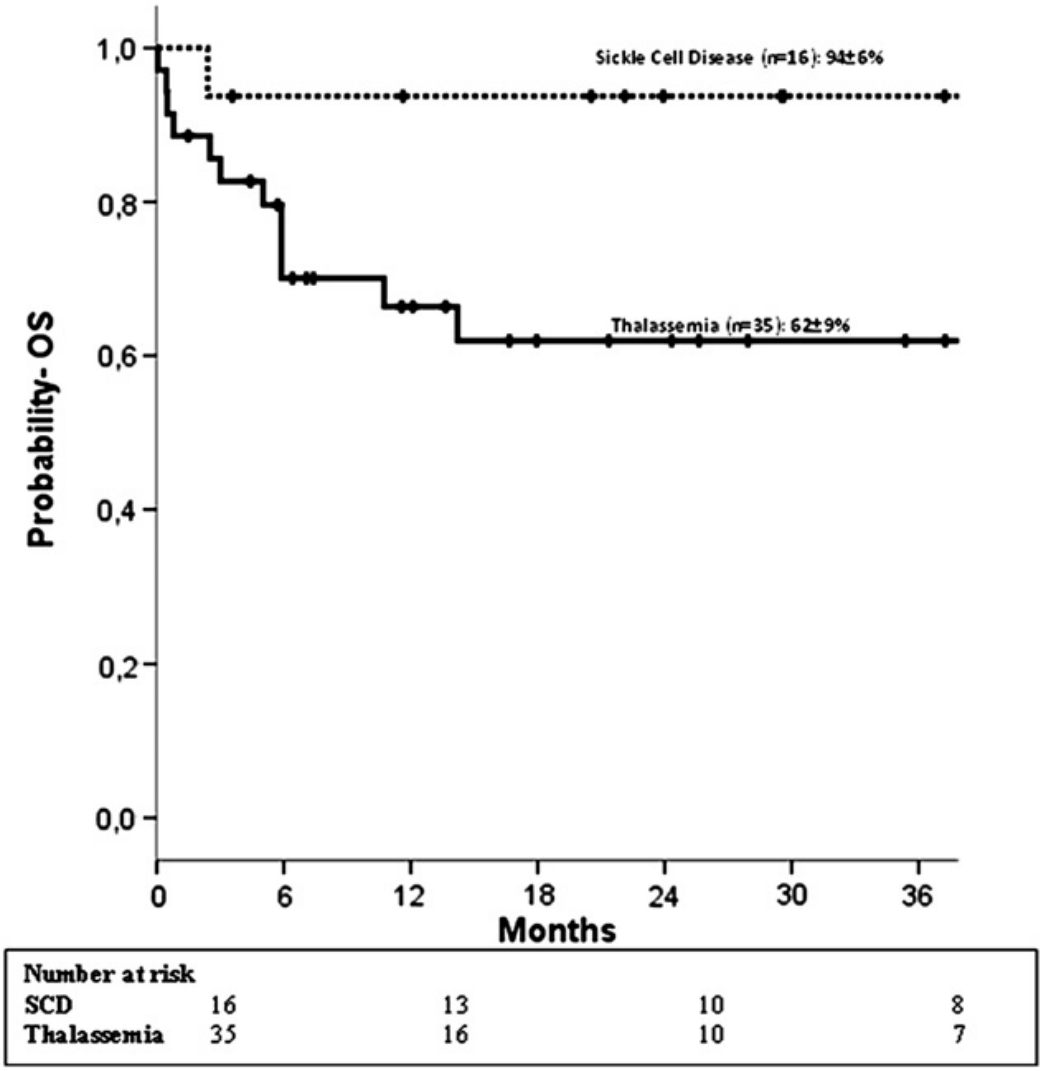

**Figure 1** Estimates of survival, thalassemia-free survival, non-rejection mortality and rejection for 515 class 1 and class 2 patients younger than 17 years who were treated with busulfan 14 mg/kg, cyclophosphamide 200 mg/kg and ± thiotepa 10 mg/kg.

Source: Lucarelli and Gaziev 2008

In experience reported by Locatelli (Locatelli and Rocha et al. 2003), of 33 patients treated for thalassemia using UCB transplantation from an HLA-matched sibling (three or fewer had an HLA-A mismatch), there were no deaths in a median follow-up of 24 months, but 7 had graft failure.

In contrast, recent experience using UCB transplantation reported by Ruggeri (Ruggeri and Eapen et al. 2011) found a lower proportion of post-transplant survival in beta thalassemia; the experience was not too different from the small experience in the Docket data.

**Figure 53: Estimated Overall Survival Following UCB Transplantation for Beta Thalassemia (and Sickle Cell Disease) – Ruggeri 2011**




Source: Ruggeri and Eapen et al. 2011

## Case reports

Case report information was provided in publications and related information in Docket documents 2006-D-0157-DRAFT-0079, -0080, and -0081.

Jaing reported on a series of five consecutive patients who received UCB for beta thalassemia major (Jaing and Hung et al. 2005a). The first case of the five was also reported separately in greater detail (Jaing and Hung et al. 2005b). The median age was 3.7 years with a range of 2.3 to 11.4 years. The oldest patient continued chelation therapy into the early post-transplantation period. The median follow-up following UCB transplant was 303 days, range 152 to 454 days. All patients achieved 100% donor chimerism and transfusion independence following transplant.

*Reviewer's Comments:*
*While it is not explicitly documented per se, this Reviewer can accept the premise that near correction of the hemoglobinopathy and elimination of transfusion dependence in beta thalassemia major does not occur spontaneously. Evidence that UCB can have that effect comes from the case reports in the literature that were submitted to the Docket. The datasets in the Docket provide a limited experience (n=8) for estimating the mortality of UCB Transplantation, but that experience raises questions about risk-benefit assessment and the comparability or the risk with other hematopoietic stem cell therapy for this disease. The 66% one-year mortality appears to be unacceptably high given the expected usually excellent short- to intermediate-term prognosis for pediatric patients with beta thalassemia major.*

### 6.7.5 Analysis of Secondary Endpoint(s)

The potential to substantiate claims for clinical benefits other than survival was not evaluated in the Docket datasets, because no disease-specific outcome data were included.

### 6.7.7 Subpopulations

The population in the Docket datasets (n = 8, with 3 deaths) was too small to permit meaningful subpopulation analyses.

### 6.7.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A proportional hazards model found no significant relationship between TNC dose and survival (nominal p = 0.71) with an estimated 4.0% *increase* in hazard for each increase of $10^7$ cells/kg. There was no patient with a dose < 2.5 x $10^7$ TNC/kg. The number of patients was too small to permit meaningful subset analysis of groups with dose above and below the median dose.

## 6.7.10 Additional Efficacy Issues/Analyses

### Published Reviews and Opinions

In a review of cord blood banking by an AAP Work Group (Work Group on Cord Blood Banking 1999), the summary of indications for allogeneic stem cell transplantation included thalassemia in the category of "effective, controversial in unrelated subjects," and those conclusions were reflected in the 2005 IOM report on cord blood (Meyer and Hanna et al., 2005). However, the AAP review did not provide references to specific data in support of that determination. The Cochrane Collaboration has not reviewed the use of stem cell transplantation in beta thalassemia, although a report on that topic is in the protocol stage. However, on the related topic of stem cell transplantation for sickle cell disease, the Cochrane Collaboration concluded:

> Reports on the use of hematopoietic stem cell transplantation improving survival and preventing symptoms and complications associated with sickle cell disease are currently limited to observational and other less robust studies. No randomized controlled trial assessing the benefit or risk of hematopoietic stem cell transplantations in children was found. Thus, this systematic review identifies the need for a multicentre randomized controlled trial assessing the benefits and possible risks of hematopoietic stem cell transplantations comparing sickle status and severity of disease in children. (Oringanje and Nemecek et al. 2010)

In support of the use of stem cell transplantation for thalassemia, the IOM report cited primary sources of Issaragrisil and Visuthisakchai et al. 1995, Goussetis and Peristeri et al. 2000, and Locatelli and Rocha et al. 2003, of which only the last contains substantial data. More recent reviews addressing the use the use of cord blood in hemoglobinopathies are found in Lucarelli and Gaziev 2008, Smith and Wagner 2009, Boncimino and Bertaina et al. 2010, Kanathezhath and Walters 2010, and Gaziev and Lucarelli 2011. Boncimino's review noted that unpublished results from the Eurocord experience suggested transplant with unrelated cord blood was "significantly inferior" to results with sibling cord blood. References cited in the various reviews in support of the effectiveness of cord blood in thalassemia are: Locatelli and Rocha et al. 2003, Jaing and Hung et al. 2005a (one of the Docket submissions discussed above), Jaing and Yang et al. 2007, a 2008 abstract by Jaing (that appears similar to the subsequent publication Jaing and Hung et al. 2011), and Jaing and Chen et al. 2010. Search of the literature identified additional primary reports of outcomes from experience with UCB in beta thalassemia: Lau and Ma et al. 1998; Jaing and Hung et al. 2005b; Jaing and Tan et al. 2008; Jaing and Hung et al. 2005b; Lisini and Zecca et al. 2008; Jaing and Hung et al. 2011; Laughlin and Kurtzberg et al. 2011; Ruggeri and Eapen et al. 2011. The evidence from these publications is described below:

## Published experience with UCB in beta thalassemia

*Lau and Ma et al. 1998 (R-UCB n=2)*
This is a report of two girls with beta thalassemia major in Hong Kong who received *related* (HLA-matched sibling) UCB transplants and became transfusion independent. The report is of interest because it included quantitative results of serial hemoglobin typing that showed HbF and $HbA_2$ both eventually falling below 5%.

*Suvatte and Tanphaichitr et al. 1998 (R-UCB n=6)*
This is a report of 69 children in Thailand who received stem cell transplantation, including 35 patients with thalassemia (beta thalassemia major or double heterozygotes with an additional β chain variant), of whom 6 received *related* (HLA-matched sibling) cord blood. Among the 35, 77% were reported to be cured, and the probability of survival was 86%. Of the 6 who received sibling UCB, two died from infection within a year of transplant.

*Locatelli and Rocha et al. 2003 (R-UCB n=33)*
This reports on a retrospective analysis of 44 patients from 22 centers worldwide who received *related* (HLA-identical sibling) UCB transplant for hemoglobinopathies, including 33 cases of beta thalassemia. Median follow-up was 24 months, and none was lost to follow-up. Of the beta-thalassemic patients, 61% were Pesaro class 1; the rest were class 2. Transfusion history was not reported. No deaths were reported; however, 7 (21%) of the thalassemia patients failed to engraft with the initial transplantation; four had subsequent BMT from the same donor, and three of these are reported “alive without disease” 3 or more years after transplant. The failure rate was higher in class 2 patients. Three of the thalassemia patients who engrafted had stable mixed chimerism (< 95% donor cells) with donor fractions between 80% and 90%. All three were reported as “alive without disease” with 1 to 2 years of follow-up. Transfusion dependence status is not described, and there were no results of hemoglobin studies. The authors noted that use of methotrexate in the GVHD prophylaxis regimen reduced the likelihood of engraftment, as did use of a conditioning regimen that did not include thiotepa.

*Jaing and Hung et al. 2005a, Jaing and Hung et al. 2005b (U-UCB n=5)*
Case reports of 5 patients with beta thalassemia transplanted in Taiwan with unrelated cord blood. These are the articles that were submitted to the Docket and that are reviewed in Section 6.7.4 above.

*Jaing and Yang et al. 2007 (U-UCB n=5)*
This is a report of 5 patients in Taiwan with beta thalassemia, ages 11 through 13, treated with double-unit unrelated cord blood transplants. One patient appears to be the same as the oldest patient previously reported in Jaing and Hung et al. 2005a. Median follow-up was 18.5 months. One patient died of pulmonary hemorrhage, 1 had autologous recovery, and 3 achieved transfusion independence. All but the patient who

had graft failure showed 100% single donor chimerism. Hemoglobin studies are not reported.

*Jaing and Tan et al. 2008 (abstract, U-UCB n=51)*
This is a brief abstract report on experience with 51 patients who received unrelated cord blood for beta thalassemia. Author affiliations are California and southeast Asia. Most of the patients received unwashed and plasma-depleted units. The abstract reports that 7 (14%) died, but also states that 38 (75%) were alive with a median follow-up of 296 days. The authors report that use of plasma-depleted units was favorably associated with transplant-related mortality, overall survival, and disease-free survival.

*Kabbara and Locatelli et al. 2008 (abstract, UCB n=42)*
This is a brief abstract report of a series of 388 patients with hemoglobinopathies who received HSCT, including 42 patients with thalassemia major who received cord blood (relatedness not specified). They reported the 5-year disease-free survival rate in thalassemia was 83% for UCB vs. 87% for BMT.

*Lisini and Zecca et al. 2008 (R-UCB n=27)*
This was a retrospective review of 106 patients given HSCT for beta thalassemia in Italy. The patients received related BMT (n=42), unrelated BMT (n=37) or *related* UCB (n=27). Median follow-up was 40 to 51 months, depending on the group; the minimum for any patient was 15 months. All transplants were identical HLA matches. For the related UCB patients, thiotepa was included in the conditioning regimen, and methotrexate was not used for GVHD prophylaxis. The overall survival was 95% and overall thalassemia-free survival (alive and transfusion independent) was 85%, but there were no deaths or graft failures in the related UCB group. The unrelated BMT group tended to have the worst outcomes regarding GVHD, engraftment, and survival. In the related UCB group, 48% achieved full donor chimerism. The remainder had mixed chimerism after discontinuation of immunosuppressants that was stable through 1 year of follow-up, and all are reported to be “disease-free.” All patients in any group who had full donor chimerism or stable mixed chimerism maintained hemoglobin in the range 9.3 to 14.7 g/dL.

*Jaing and Chen et al. 2010 (cf. Jaing and Hung et al. 2011)*
This article reports on 45 patients treated in Taiwan with unrelated UCB for nonmalignant conditions, including 32 patients with transfusion-dependent thalassemia. The patients with thalassemia appear to be a subset of those described in the thalassemia-specific publication (Jaing and Hung et al. 2011) reviewed below.

*Jaing and Hung et al. 2011 (U-UCB n=35)*
This is a report of a prospective study of 35 patients with transfusion-dependent thalassemia who received unrelated UCB in Taiwan. Most had beta thalassemia major, but 4 were double heterozygotes with an additional β chain variant. Median age was 5.5 years. No patient had a splenectomy. Pesaro class was not reported in this publication, but in subsequent symposium proceedings (Laughlin and Kurtzberg et al.

2011), it was reported that 63% of patients were Pesaro class 1. All had conditioning regimens that involved busulfan, cyclophosphamide, and antithymocyte globulin. Cyclosporine and methylprednisolone were used for GVHD prophylaxis. HLA matching was full for 15%, one mismatch for 31%, two mismatched for 52%, and 3 mismatched for 2%. Mean dose was 7.8 x $10^7$ TNC/kg; 26% of patients received double units initially. Four deaths were reported. With a median follow-up of 36 months, the estimated overall 5-year survival was 88% ± 7% (SE), and the estimated 5-year thalassemia-free percentage after first transplant was 74% ± 7%. Including second transplants, 30 (86%) were alive and transfusion independent. Hemoglobin studies were not reported.

*Laughlin and Kurtzberg et al. 2011 (cf. Jaing and Hung et al. 2011)*
These symposium proceedings include a description of a session report by T. H. Jaing that appears to be the same population reported in Jaing and Hung et al. 2011, but it is of note that this report provides the additional information that 63% of patients were Pesaro class 1.

*Ruggeri and Eapen et al. 2011 (U-UCB n=35)*
This is an analysis of cases of unrelated UCB used for sickle cell disease and thalassemia as reported to Eurocord, the National Cord Blood Program, the New York Blood Center, and the Center for International Blood and Marrow Transplant Registry between 1996 and 2009. Duplicate reports were removed. The review included 35 unique reports of patients with thalassemia. Median age was 4 years. Pesaro class was unknown for the majority of patients. All but 3 received a conditioning regimen that included antithymocyte globulin. HLA matching was full for 14%, one mismatch for 40%, two mismatches for 43%, and 3 mismatches for 3%. There were 12 deaths, 7 in patients that had engraftment. Median follow-up of survivors was 21 months. At 15 months and beyond the estimated overall survival was 62% ± 9% (SE), and disease-free survival was 21% ± 7%. Survival and disease-free survival proportions were about 30% higher in patients with sickle cell disease than in patients with thalassemia. [Despite coincident number (35) with the report of Jaing and Hung et al. 2011, it appears that the different reporting agency, median age, HLA matching, and outcomes all point to this not being the same population.]

The results led the authors to make the following statement in their discussion:

> Taken together, the transplantation strategies using unrelated CB [cord blood] as the stem cell source is suboptimal for patients with hemoglobinopathy. Graft failure remains a major limitation to success, and the continuing use of CB for this disease must be discouraged outside of well-designed novel clinical trials. (Ruggeri and Eapen et al. 2011)

Additional reports of single cases or small case series were identified but not subject to detailed review due to their small size: Issaragrisil and Visuthisakchai et al. 1995; (n=1, sibling UCB); Wagner and Kernan et al. 1995 (n=2, sibling UCB); Chik and Shing et al.

1996 (n=1, sibling UCB); Gluckman and Rocha et al. 1997 (related and unrelated UCB; 5 thalassemia patients as part of much larger group, but thalassemia-specific results not provided); Goussetis and Peristeri et al. 2000 (n=3, BMT plus sibling UCB); and Hall and Martin et al. 2004 (n=1).

# 9 Appendices

## 9.1 Literature Review/References

### 9.1.1 Literature Searches

Literature searches were conducted in an effort to identify historical experience that could be used as control experience for comparing results of the UCB transplant experience from the Docket datasets. The general search strategies that were used are presented below.

#### Hurler Syndrome

The following PubMed searches were used:
mucopolysaccharidosis i [MeSH Terms] AND natural history n=9
mucopolysaccharidosis i [MeSH Terms] AND clinical trial [Publication Type] n=31
(The broader search for "clinical trial" was used, because a search using "…AND controlled clinical trial [Publication Type]" produced only 1 citation.)

#### Krabbe Disease

The following PubMed searches were used:
leukodystrophy, globoid cell [MeSH Terms] AND natural history n=5
leukodystrophy, globoid cell [MeSH Terms] AND clinical trial [Publication Type] n=4
(The broader search for "clinical trial" was used, because a search using "…AND controlled clinical trial [Publication Type]" produced no citations.)

#### X-linked Adrenoleukodystrophy

The following PubMed searches were used:
adrenoleukodystrophy [MeSH Terms] AND natural history n=11
leukodystrophy, globoid cell [MeSH Terms] AND clinical trial [Publication Type] n=32
(The broader search for "clinical trial" was used, because a search using "…AND controlled clinical trial [Publication Type]" produced only 5 citations.}

#### Primary Immunodeficiency

The following PubMed searches were used:
(immunologic deficiency syndromes [MeSH Terms] NOT hiv infections [MeSH Terms]) AND natural history n=112
(immunologic deficiency syndromes [MeSH Terms] NOT hiv infections [MeSH Terms]) AND controlled clinical trial [Publication Type] n=66

(The narrower search for *controlled* clinical trials was used, because a search using "…AND clinical trial [Publication Type]" produced 568 citations.
Although it is possible to restrict searches using "congenital" as a subheading, a search using "…AND congenital[sh] AND natural history" produced no citations, and a search using "…AND congenital [sh] AND clinical trial [Publication Type]" produced only 1 citation.)

## Bone Marrow Failure

The following PubMed searches were used:

anemia, aplastic [MeSH Terms] AND natural history n=31
anemia, aplastic [MeSH Terms] AND controlled clinical trial [Publication Type] n=35

(The narrower search for "controlled clinical trial" was used, because a search using "…AND clinical trial [Publication Type]" produced 427 citations.)

## Beta Thalassemia

The following PubMed searches were used:

beta thalassemia [MeSH Terms] AND natural history n=23
beta thalassemia [MeSH Terms] AND controlled clinical trial [Publication Type] n=48

(The narrower search for *controlled* clinical trials was used, because a search using "…AND clinical trial [Publication Type]" produced 303 citations.)

## Additional Sources

Several documents submitted to the Docket provided references to publications; these were scanned for relevant titles suggesting natural history, clinical trial data, or related analyses. For example, document 2006-D-0157-DRAFT-0047 (repeated in -0050 and -0082) by Dr. Kurtzberg included a bibliography, and document 2006-D- 0157-DRAFT-0064 (repeated in -0065) from NYBC included citations along with comments on indications.

For Hurler syndrome, Krabbe disease, X-linked adrenoleukodystrophy, and beta thalassemia, the disease overviews in Online Mendelian Inheritance in Man (OMIM) were used to identify an additional list of references to review in an attempt to identify relevant natural history data or controlled studies for those conditions.

Less systematic PubMed searches were also used in an attempt to expand the identification of pertinent publications. For example, if the search for a reference in PubMed produced related articles from the search or generated a PubMed suggestion list, promising leads were also pursued. In all cases, the citations listed in the publications from the other search methods were scanned to identify any additional publications that could be contributory.

## Use of Online Publications

Publications that were only available online (such as publications from CIBMTR.org that were not available as journal articles) were not relied upon as sources of data for this review. However, online information was referred to for general information (e.g., Cochrane review, OMIM, UpToDate) and as potential leads to identify relevant published information.

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